Author's response to reviews

Title: Cardiovascular risk factor treatment targets and renal complications in high risk vascular patients: a cohort study

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Author's response to reviews: see over
Dear Dr. Jigisha Patel,

Thank you for considering the revised version of our manuscript entitled “Cardiovascular risk factor treatment targets and renal complications in high risk vascular patients: a cohort study” for publication in BMC Cardiovascular Disorders. We are grateful to the referees and the Editor for pointing out some important clarifications and changes needed in the paper. We have thoughtfully taken into account these comments and have addressed the reviewers’ concerns point by point in the following pages.

We consider the comments very constructive and have been especially useful in restructuring the manuscript.

We hope all these changes fulfill the requirements to make this manuscript acceptable for publication in BMC Cardiovascular Disorders.

Looking forward to hearing from you soon.

Sincerely yours,

Sharmini Selvarajah
Response to Reviewer Demetrios Vlahakos’ comments:

1. The reviewer was concerned that using RAS inhibitors as a treatment goal instead of decreases in albumin excretion was misleading to the readers.

   - The reviewer is right to point out that decrease in albumin excretion is a desired goal. We feel we need to express ourselves more clearly in our choice of RAS inhibitor use as a goal for treatment target. The benefits of RAS inhibitors are multiple fold; blood pressure reduction, independent effects on artery stiffness, decrease in albumin excretion and delay in progression/development of albuminuria. In clinical practice, the use of an RAS inhibitor is continued even in patients who do not show a decrease in albumin excretion. This is because, although a regression or decrease may not be seen, a delay in time to deterioration may occur. On an individual basis in clinical practice, the delayed time to albuminuria progression due to RAS inhibitor use cannot be determined. Aside from this, irrespective of its type of effects on albuminuria (delay or regression), RAS inhibitors are the drug of choice and patients are maintained on therapy unless they are unable to tolerate it. Therefore, the authors felt that appropriate treatment for albuminuria using RAS inhibitors should be a desired target for good clinical practice.

   - The reviewer’s concern that 78% achieved the target for albuminuria is actually a reflection of good clinical practice of RAS inhibitor prescription.

   - We have amended the methods section (as described below) to include the reasoning behind our choice of target and to address the reviewer’s concerns.

   - “For albuminuria status, the target to achieve was no micro-albuminuria. For those with albuminuria (micro-albuminuria or proteinuria), the desired target was the appropriate choice of therapy for albuminuria; treatment with either an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB). The choice of renin-angiotensin system (RAS) inhibitor use as a treatment goal is due to its effects on albuminuria, independent of blood pressure lowering. RAS inhibitors either improve albuminuria by reducing excretion (regression or stabilization) (19-21) or by delaying the time to progression (22).”

2. The reviewer felt that the lack of statistical findings for diabetics is due to the short follow up duration. We agree with the reviewers comment. We have added the reference quoted by the reviewer and modified the section on limitations as follows.

   - “The duration of follow up may be insufficient for ESRF development in many patients. In the UKPDS studies, development of renal endpoints occurred only in 0.8% after a median of 10 years (34). Aside from this, the number of events that occurred was small, 81 in total and in diabetics 28. This may explain the
lack of power in proving statistical significance, except for the tests for trends.”

3. The reviewer has mentioned that the pathophysiological mechanisms of the endpoints are different. Again we agree with the reviewer and have added this as a strength of the study detailed below. This is because for an individual patient of high risk, goals for prevention of CVD are set by clinical practice guidelines. Doctors aim to achieve treatment targets, without the knowledge of the type of complication a patient will suffer in the future. Therefore, irrespective of the pathophysiological mechanism, these treatment targets are beneficial in reducing renal complications.

- “These hard endpoints reflect different pathophysiological mechanisms. End stage renal failure may be caused by both micro and macrovascular changes whereas renal vascular disease is caused by macrovascular changes. Despite these differing pathophysiological mechanisms, these findings are suggestive that the same treatment targets reduce their risk of development.”

4. The reviewer was concerned that use of beta blockers and RAS inhibitors were associated with treatment targets being achieved. The use of beta blockers in this case is associated with the higher rates of coronary artery disease (Baseline Table 2). In this study, about 47% of those prescribed beta blockers had ischaemic heart disease. Only 12% of those prescribed beta blockers were due to hypertension. Aside from this, up to 50% of the study population were recruited before 2004. This may help explain the use of beta blockers as well. These values given here hopefully explain the values seen in the baseline table. In the original manuscript, we had not described in detail the specific types of drugs used to achieve targets. Unfortunately, we do not have information on the types of beta blockers used. The following sentence has been added to the results section describing the reasons for beta blocker prescription;

- “About 47% of those prescribed beta blockers had ischaemic heart disease. Only 12% of those prescribed beta blockers were due to hypertension.”

5. We are grateful for the reviewer’s comments numbered 5 to 7 which provides supportive information for this manuscript. These have been added to the discussion section with the reference quoted.

- “With increasing treatment targets achieved, a lower haemoglobin concentration level was seen. However, it was not associated with poorer outcomes. This may be a result of more liberal use of RAS inhibitors, which decreases erythropoiesis (27).”

- “There was no optimal number of cardiovascular risk factor treatment targets to achieve. The risk of renal complications decreased linearly as more targets were attained; consistent with the notion that no J-curve exists for renal outcomes.”
"More patients achieving the target for diastolic blood pressure than for systolic blood pressure is also consistent with other studies (29). This is probably reflective of older, stiffer arteries which is expected in high risk patients, and not because therapies used were more effective in lowering diastolic blood pressure."

6. We are very grateful for the valuable time and effort spent by the reviewer on our manuscript. We are also very appreciative of the constructive comments which are very clinically relevant. We feel that the comments given have provided us with the opportunity to improve our paper.
Response to Reviewer Rajiv Chowdhury’s comments:

1. The reviewer has suggested a major revision of the analysis excluding patients with renal insufficiency or atherosclerosis to determine if similar decreases in risk of renal outcomes are seen with increasing treatment targets.

   • We agree that this is an important area that requires further research. However, this cohort study had a median duration of 4.21 years. We have noted that this duration may be insufficient for ESRF development. The UKPDS study showed that only 0.8% of their study population developed ESRF after a median of 10 years. We feel that changing the main analyses to exclude patients without renal insufficiency would be beyond the scope of this manuscript for the following reasons:
     
     i. Excluding renal insufficiency patients would lead to a severe reduction in events (since these are rare outcomes).
     
     ii. The strength of this study is that, even in patients with renal insufficiency, time to endpoints can be delayed with attainment of two or more targets.

2. The reviewer was concerned that self-reported outcomes is a limitation of the study, especially since the outcome reno-atherosclerotic disease requiring intervention was not clearly defined.

   • The reviewer is right to point out that self reported outcomes are usually a limitation. However, for this study, we do not feel that this is a limitation for our study because of the following reasons:

     i. Information on all hospitalization and outpatient clinic visits were requested. All hospitalizations were reconfirmed through medical records. Patients who did not want to fill the questionnaires were asked if study investigators could contact their general practitioners and this was successful in maintaining good follow up rates (up to 98%).

     ii. The two outcomes of interest are severe conditions. End stage renal failure treatment requires haemodilaysis or renal transplantation. Reno-atherosclerotic disease requiring intervention meant stenting or bypass graft surgery of the renal arteries. All of these required hospitalization.

   • Although we feel this was not a limitation, we are grateful for the comment by the reviewer. We have now modified the methods section to better explain the determination of our outcomes (see below).

   • “During the follow up period, outcomes were determined through questionnaires biannually. Participants provided information on hospitalization and clinic visits. Original source documents were reviewed if a hospitalization or clinic visit was reported. All hospital discharge letters and
results of related laboratory and radiological examinations were collected. Each event was classified according to a standard operating procedure. All endpoints were adjudicated by three members of the SMART Endpoint Committee, comprising of physicians from different departments.”

- We acknowledge that our description of outcome reno-atherosclerotic disease requiring intervention was not sufficiently clear. We have amended the methods section to define our outcome more clearly, as below.

- “Renal outcomes were defined as a composite endpoint consisting of end stage renal failure requiring renal replacement therapy and reno-atherosclerotic disease requiring intervention; either arterial stenting or bypass grafting.”

3. The reviewer requested separate analysis of the study excluding all patients with missing waist circumference and HbA1c values.

- While we too are disappointed with the fact that we have some missing values, we feel that separate analyses excluding missings for waist circumference and HbA1c is not appropriate. Excluding patients with missing values (complete case analysis) reduces the effective number of patients in the study. There is strong evidence that complete case analysis gives biased results [1, 2]. Aside from that, excluding these patients will lose valuable information on the other 5 treatment targets (blood pressure, cholesterol levels and albuminuria). Waist circumference was not a confounder in multivariable testing. Aside from this, due to the low number of events in diabetics, the trend is not statistically significant even with imputation for HbA1c.

4. The reviewer has suggested that the multivariable analysis (Table 3) include other factors such as smoking, alcohol consumption, obesity etc.

- We agree with the reviewer that other important covariates should be included. In this study, as mentioned in the statistical analyses section (copied below) these factors were tested to determine inclusion in the final model.

- “Confounders were selected a priori for testing based on literature. Variables selected were age, sex, waist circumference, history of coronary artery disease, cerebrovascular disease, peripheral arterial disease and renal disease, smoking status (never, former, current), alcohol consumption (never, ever, recently stopped, current), haemoglobin levels, albuminuria status (no, micro-albuminuria, overt proteinuria) and estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) formula. These were then determined to be included in the final model if there was a change in the hazard ratio (HR) estimate of more than 10 percent when compared to the crude estimate [3].”
• In the final model, only important confounders that changed the HR by more than 10% were included. We chose these important confounders because the number of actual events is too small. If we adjusted for a large number of covariates (irrespective of importance), it would lead to unstable modelling and inaccurate results. This is the approach we teach at the Julius Center during our MSc clinical epidemiology course.

5. The reviewer would like information specifically on the number of excluded non-Dutch speakers. The reviewer was concerned that the risk of the outcomes would be different in this population because of limited access to healthcare and lower adherence to medication.

• There were 2800 patients who were excluded, including the group who is not fluent in Dutch. Unfortunately we do not have precise estimates of the reasons for exclusion. Out of those that did report a reason, only 3 were excluded because they were not fluent in Dutch.

• This is a cohort study. This non response, as is every non response in every study, is likely to be selective. That is related to either the determinant or the outcome. Non response in general affects prevalence rates, and when the interest is in true incidence, it does affect the incidence rates. Generally, the prospective relations under study found in cohorts despite non response are not severely affected by the non response. Therefore we feel that also our estimates are valid.

6. The reviewer was concerned that these results are based on a shorter than required duration and should be mentioned as a limitation in the study.

• We agree with the reviewer and have amended the discussion section as below.

• "The duration of follow up may be insufficient for ESRF development in many patients. In the UKPDS study, development of renal endpoints occurred in only 0.8% after a median of 10 years [4]. Aside from this, the number of events that occurred was small, 81 in total and in diabetics 28. This may explain the lack of power in proving statistical significance, except for the tests for trends. A longer follow up duration would provide more accurate estimates and therefore stronger evidence."

7. The reviewer has suggested that in addition to Table 3, we have an additional table which collapses the categories into 3 broad categories (<=1; 2; and >=3 treatment targets), in order to have more events and patients in them.

• It is true that combining the categories 4 and 5 would result in more events and patients in the 3rd category. However, we feel that having an additional table presenting the combined categories would not provide readers with new information, but would lead to a loss of information. The lack of a J curve of
risk decrease as numbers of targets achieved increased (as seen in Table 3) would not be observed.

8. We sincerely thank the reviewer for his valuable time and insights into this manuscript. We appreciate the opportunity to explain our study further and to make it more relevant.

References
