Author’s response to reviews

Title: Renal function at the time of a myocardial infarction maintains prognostic value for more than 10 years

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Author’s response to reviews: see over
Response to referees’ comments

We appreciate the referees’ comments and we have been able to respond to most of the points. We believe that the comments and suggestions made by the referees have improved the manuscript, and hope that the referees and the editors are satisfied with the revised version of the manuscript.

Below are our point-by-point responses, typed in green color, and in case of changes were made to the manuscript, these are specified by page and line numbers. Additions to the text are highlighted in blue color and deletions are highlighted in red color and strikethrough.

Referee 1

Reviewer BMC

In the present investigation the Authors prospectively examined the importance of renal function by estimated GFR (eGFR) and se-creatine as an independent long-term prognostic factor in 6653 consecutive MI patients screened for entry in the Trandolapril Cardiac Evaluation (TRACE) study. The Authors concluded that one estimate of renal function (by means of eGFR) is a strong and independent long-term prognostic factor for 10-12 years following a MI.

Several questions may be raised:
The authors should assessed whether the prognostic significance of renal function is different in MI patients submitted to revascularization in respect to those not revascularized.

Author's Response: No patients were revascularized by PCI acutely or subacutely since this treatment was not routine at the time of the study (1992-1994). The proportion of patients treated with trombolysis varied according to eGFR as illustrated in table 1. In order to examine whether the prognostic significance of renal function was different in patients revascularized with thrombolysis, we performed an interaction analysis between renal function and trombolysis. We found an significant interaction between cregroup and thrombolysis with a p-value of 0.007. The overall hazard ratio was 1.374 (CI 1.289-1.464) with a hazard ratio in the group not treated with thrombolysis of 1.367 (CI 1.281-1.460) and 1.149 (CI 1.030-1.281) in the group treated with trombolysis. Similarly, an interaction was seen between eGFRgroup and thrombolysis with a p-value of 0.001. The overall hazard ratio was 1.242 (CI 1.194-1.292), with a hazard ratio of 1.235 (CI 1.186-1.287) in the group not treated with thrombolysis and 1.128 (CI 1.068-1.191) in the group treated with thrombolysis. In conclusion, the prognostic significance was greatest in the group not treated with thrombolysis, but as can be seen from the numbers, the interaction was not very large. We added the following text to the results section:

Current manuscript (page 9, line 20 to page 10, line 7): “In order to examine whether the prognostic significance of renal function was different in patients revascularized with thrombolysis, we performed an interaction analysis between renal function and trombolysis. We found a significant interaction between creatinine groups and thrombolysis with a $p$-value of 0.007. The overall hazard ratio was 1.374 (CI 1.289-1.464) with a hazard ratio in the group not treated with thrombolysis of 1.367 (CI 1.281-1.460) and 1.149 (CI 1.030-1.281) in the group treated with trombolysis. Similarly, an interaction was seen between eGFR group and thrombolysis with a $p$-value of 0.001. The overall hazard ratio was 1.242 (CI 1.194-1.292), with a hazard ratio of 1.235 (CI 1.186-1.287)

What is the novelty in the results of the present investigations.

Author's Response: The novelty of our results is the description of the prognostic effect of renal function in 2-year intervals with a very long follow-up period. This makes it possible to document the loss of prognostic significance of a risk factor in the very long-term. It might be argued that this information is of lesser interest for renal function, which is frequently updated by creatinine measurement, than for other risk factors for example systolic function by echocardiography or diabetes, which is updated more rarely. We have added the following text to the discussion:

Current manuscript (page 13, line 24 to page 14, line 2): “The novelty of our results is the description of the prognostic effect of renal function in 2-year intervals with a very long follow-up period. This makes it possible to document the loss of prognostic significance of a risk factor in the very long-term”.

Current manuscript (page 15, lines 10-13): “It might be argued that the long-term prognostic information is of lesser interest for renal function, which is frequently updated by creatinine measurement, than for other risk factors, for example systolic function by echocardiography, which is updated more rarely”.

References should be updated and discussed.

Author's Response: We have included the mentioned references in the reference list and added the following paragraph to the discussion:

Current manuscript (page 12, line 16 to page 13, line 1): “Several recent papers have examined the prognostic role of renal function in MI patients. One study examined the prognostic significance of an acute worsening of renal function among patients hospitalised for MI surviving to hospital discharge. With a follow-up of at least 4 years, worsening renal function was independently associated with diabetes, left ventricular systolic dysfunction and a history of chronic kidney disease. After adjustment for factors associated with worsening renal function and long-term mortality, worsening renal function was independently associated with a higher risk of death. In another study, the prognostic significance of chronic kidney disease and acute kidney injury on acute coronary syndrome was reviewed. This study stressed the importance of early measurement and monitoring of renal function, which is probably standard of care in most institutions”.

Referee 2

Major Compulsory Revisions

1) The correction factor for women is wrong – it should be 0.742. Moreover the authors do not comment why they did not use the correction factor for race.
Author's Response: The correction factor was mistyped and has been corrected. A correction factor of 0.742 has been used in all calculations. We corrected the following:

Current manuscript (page 6, lines 7-8): “For women the product of this equation was multiplied by a correction factor of 0.7042”.

Author’s response: We did not use a correction factor for race because all included patients were Caucasian. We added the following text to the methods section:

Current manuscript (page 6, lines 8-9): “We did not use a correction factor for race because all included patients were Caucasian”.

2) What is the addition information from the Landmark analysis compared to the subsequent Cox regression analyses? Moreover I do not find any statistical test telling the reader if the difference between the 4 different eGFR-groups/2 years is statistically significant per each 2-year interval or not. The authors claim that “the Landmark analysis demonstrated that eGFR continued to have prognostic effect until 16 years of follow-up” and this is stated in the study title. I am not sure this conclusions can be made.

Author's Response: The referee has a valid point. The landmark analysis is a graphical presentation of the prognostic significance of eGFR groups in 2-year periods, adjusted for age and gender. The precise hazard ratios for the landmark model are as follows:

<table>
<thead>
<tr>
<th>Follow-up period, years</th>
<th>0-2</th>
<th>2-4</th>
<th>4-6</th>
<th>6-8</th>
<th>8-10</th>
<th>10-12</th>
<th>12-14</th>
<th>14-16-</th>
<th>16-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard ratio</td>
<td>1,456</td>
<td>1,289</td>
<td>1,165</td>
<td>1,131</td>
<td>1,244</td>
<td>1,201</td>
<td>1,109</td>
<td>1,125</td>
<td>1,043</td>
</tr>
<tr>
<td>Confidence interval</td>
<td>1,387-1,529</td>
<td>1,186-1,400</td>
<td>1,060-1,280</td>
<td>1,023-1,252</td>
<td>1,118-1,383</td>
<td>1,067-1,352</td>
<td>0,968-1,271</td>
<td>0,976-1,298</td>
<td>0,832-1,308</td>
</tr>
</tbody>
</table>

To clarify, we have added the following text to the results section:

Current manuscript (page 8, lines 14-19): “Estimation of renal function has prognostic significance for up to 16 years following MI, even without adjustment for changing values of se-creatinine. Landmark analyses of 2-year periods shows that the statistic significance disappears after 12 years of follow-up, but hazard ratio is almost the same in the following years, so the lack of significance in this period is probably a result of lack of power. The hazard ratio is close to 1.00 only after 16 years of follow-up”.

We have changed the title:

Current manuscript (page 1, lines 1-2): “Renal function at the time of a myocardial infarction maintains prognostic value for more than 1046 years”.

3) Three Cox regression analyses were done, the first a crude model, the second a sex and age-adjusted model and the third a multivariable adjusted model. One important finding seem to be that eGFR 60-75 ml/min was not independently associated to higher risk of 17-year mortality compared eGFR >75 ml/min (reference group) whereas eGFR 45-60 ml/min was associated to 19% higher risk and eGFR < 45 ml/min to 72% higher risk compared to the reference group. I do not find these numbers in table 2 or anywhere else in
the tables and figures but it is not stated anywhere that “data is not shown”. Is this an analysis from the whole 17-year period?

**Author's Response:** This is an analysis of the whole 17-year period and we have chosen to show these data in the results section and not in tables and figures. To clarify, we have added the following text to the results section:

**Current manuscript (page 9, lines 3-7):** “When using eGFRgroup 1 (normal renal function) as reference in the model incorporating all covariates in the whole follow-up period, estimated GFR was a significant prognostic factor in eGFRgroups 3 (hazard ratio 1.19, CI 1.09-1.30) and 4 (hazard ratio 1.72, CI 1.56-1.91) but not in eGFR group 2 (hazard ratio 0.99, CI 0.91-1.07)”.

4) From which table or figure can I draw the conclusions that “eGFR was a prognostic factor for 12 years and s-creatinine for 10 years”? My guess is table 2 where the hazard ratios regarding eGFRgroup are statistically significant up to 12 years after MI with borderline significance up to 16 years after MI and hazard ratios regarding s-creatinine group are statistically significant up to 10 years after MI, with borderline significance up to 12 years after MI (with exception of the period 6-8 years). This contradicts the next sentence “Neither s-creatinine, nor estimated GFR were significant predictors in the follow-up period from 6-8 years” (for which I find no support in tables or in figures).

**Author's Response:** This information is indeed displayed in table 2. eGFR and cregroup was significant prognostic factors of all-cause mortality for 12 and 10 years respectively with the exception of the follow-up period from 6-8 years where statistical significance was not reached, as can be seen from the confidence intervals. To clarify, we have changed the text:

**Current manuscript (page 9, lines 7-9):** “eGFR was a prognostic factor for 12 years and s-creatinine for 10 years, with the exception of the follow-up period from 6-8 years where significance was only borderline. Neither s-creatinine nor estimated GFR were significant predictors in the follow-up period from 6-8 years.”

5) Figures 3-4 include the same information as table 2.

**Author's Response:** We chose to display selected part of the data in table 2 as graphs in order to provide the reader with a more comprehensive overview of our data. We have omitted figure 3. Figure 4 (now figure 3) can be omitted if so desired by the editors.

6) Numbers of patients/two years are missing in Table 2 and in all figures and should be added to tell the readers how many survivors there are left per 2-year step.

**Author's Response:** We have added the number of patients/two years to table 2 and the figures.

7) Information about therapy on arrival, at hospital and at discharge is poorly described and is lacking in tables and in the subsequent multivariable analyses. We know from previous studies, for example from the Swedish SWEDEHEART register (Szummer et al) that the lower the eGFR, the less intensive is the treatment. In this study, this is obvious regarding thrombolytic therapy. Other therapies than thrombolysis such as evidence based medicine at discharge, thus should have been included in the multivariable analyses. Therapies should have been shown in a table together with information about;

- How many patients underwent coronary angiography or CABG? Surely there are differences between different CKD groups.
- What was the difference between the CKD groups in rate of complications
during hospital care and re-infarctions and new revascularization procedures after discharge?

In summary, the results and statistical sections must be much clearer for the reader. Information is missing in tables and figures (but not clearly written that data is not shown) and much information in the tables and figures is never commented anywhere in the results or in the discussion. Several tables and figures could be omitted and table 2 is very busy and could be simplified. I suggest that model 2 in table 2 is omitted together with the bottom 3 lines which could be shown only in figure 4 which could be shown as a Forest plot. Figure 2-3 could be omitted. On the other hand, information about therapies, revascularization procedures and complications is missing in the tables.

Author's Response: We do not have information regarding how many patients underwent coronary angiography or CABG during hospital stay or later. This treatment was not routine at the time of the trial (1992-1994). We have included the following information to table 1: The proportion of patients receiving digoxin and ACE inhibitors at discharge, the proportion of patients with ventricular fibrillation, ventricular tachycardia, atrial fibrillation during hospital stay. There were few patients with recurrent MI (N=198, 3.72 %) or pulmonary embolism (N=27, 0.27 %). Only 178 patients (3.33 %) were receiving antiarrhythmic therapy at discharge. We have omitted model 2 in table 2 in order to simplify the table as suggested. Figure 3 has been omitted.

We have added the following text to the discussion:

Current manuscript (page 15, lines 2-6): “We do not have information regarding how many patients underwent coronary angiography or CABG during hospital stay or later. This treatment was not routine at the time of the trial (1992-1994). As a result, we cannot evaluate whether the frequency of invasive treatment differ in the eGFR groups”.

We have added information regarding the definition of medical treatment and complications to the figure 1 legend.

We have added the following text to the results section:

Current manuscript (page 8, lines 4-6): “There were few patients with recurrent MI (N=198, 3.72 %) or pulmonary embolism (N=27, 0.27 %). Only 178 patients (3.33 %) were receiving antiarrhythmic therapy at discharge”.

We did not include information regarding complications because of the risk of immortal time bias. Since clinicians have varying thresholds for initiating medical therapy, we did not include information regarding the medical treatment at discharge in the multivariable analyses because this could make the interpretation of results very complex and difficult. We have added the following text the results section:

Current manuscript (page 8, line 21 to page 9, line 2): “In the multivariable analyses we included demographic factors, comorbidities and information regarding thrombolytic therapy. We did not include information regarding complications because of the risk of immortal time bias. Since clinicians have varying thresholds for initiating medical therapy, we did not include information regarding the medical treatment at discharge in the multivariable analyses because this could make the interpretation of results very complex and difficult”.

In addition, we have added the following text to the discussion section:
Current manuscript (page 13, lines 18-20): “With declining renal function, patients in our study were more often women, were older and had a greater frequency of comorbidities. This is in accordance with previous studies”.

Minor Essential Revisions

1) It would have been preferable to incorporate eGFR in the multivariable analyses (table 2) as a continuous variable and show hazard ratios for death per 10 ml/min eGFR change. The alternative would have been to use CKD stage as a categorical variables and use stage 1 or 1-2 combined (or above 75ml/min as the authors did) as reference group.

Author's Response: We chose to to use eGFR as a categorical variable in the form of eGFRgroup, incorporating the guidelines of the National Kidney Foundation. This approach was previously used in a landmark paper (Anavekar NS, McMurray JJ, Velazquez EJ, Solomon SD, Kober L, Rouleau JL, White HD, Nordlander R, Maggioni A, Dickstein K et al: Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. N Engl J Med 2004, 351(13):1285-1295).

2) How were the variables in the multivariable analyses chosen? Why are not Killip class, NYHA class, therapy at hospital, therapy at discharge and revascularization procedures taken into account as well as smoking and previous stroke, at least some of which seem to be available according to table 1? Why is age included in 10 years intervals in this study with many patients and events?

Author's Response: The basis for choosing the variables in the multivariable analyses have been described above (major revisions, question 7). Age was included as a continuous variable in the multivariable analyses.

Discretionary Revisions

1) S-creatinine on arrival may not represent steady state as the MI patient may suffer from cardiogenic shock or pulmonary oedema in the acute phase. These patients were included long before primary PCI was standard therapy for STEMI patients, but there is still important to know if any of these patients were taken directly to the cath lab. There is a risk that medication (for example in the ambulance or at cath lab) or coronary angiography prior to the analysis may have affected the value. Moreover, in order to diagnose a patient as having RI the eGFR should be < 60 ml/min during at least 3 months. Thus, there are several reasons why a sensitivity analysis would have been useful with s-creatinines analysed from before or from after the acute event. Anyhow the study show that even just a single s-creatinine taken on arrival bears prognostic information long time after the acute event and this is an important finding.

Author's Response: No patients were taken directly to the cath. lab. in this study. No patients were given medication in the ambulance which could worsen renal function. As can be seen from table 1, the vast majority of patients were in Killip class I or II, so very few patients had cardiogenic shock or pulmonary oedema during hospitalization.

2) The National Kidney Foundation recommends classification of renal dysfunction (K/DOQI clinical practice guidelines) into the following; CKD stage 1 (#90 ml/min), 2 (60-89 ml/min), 3 (30-59 ml/min, which could be subdivided into 3a, 45-59 ml/min and 3b, 30-44 ml/min), 4 (15-29 ml/min) and 5 (<15 ml/min or in dialysis) using the MDRD formula. Without information about urine status, renal insufficiency is defined as eGFR<60 ml/min more than 3 months. ACS patients do seldom belong to stage 1 and among women with ACS the majority belongs to stage 3-5. Why did the authors use other cut off values, as quite many patients
are included? Patients with s-creatinine > 200 µmol/L were excluded in TRACE, but as I understand are included here. Why were patients in stage 3b, 4 and 5 analysed together? Wouldn’t it have been more convenient to present data using the well-known CKD stages?

Author's Response: We divided eGFR into groups used previously (Anavekar NS, McMurray JJ, Velazquez EJ, Solomon SD, Kober L, Rouleau JL, White HD, Nordlander R, Maggioni A, Dickstein K et al: Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. N Engl J Med 2004, 351(13):1285-1295), incorporating the guidelines of the National Kidney Foundation. We believe that further dividing groups into subgroups would make the results less operational. Patients with se-creatinine>200 µmol/L were excluded from the TRACE study (randomized patients) but are included in our analyses, which comprises the screened patients.

3) What was the point of analyzing s-creatinine groups, and how was the cut off values chosen? Estimated GFR according to the MDRD formula is well known to be superior compared to s-creatinine values but have some weaknesses, for example underestimating eGFR in women and in patients with normal kidney function. If the authors wanted to strengthen their findings maybe it would have been better to add another eGFR method, for example the Cockcroft Gault formula. Estimated GFR based on the CG formula is found to be a stronger predictor of outcome in MI patients than eGFR based on the MDRD formula in one study (Szummer et al) and it would have been interesting to have results also from this study.

Author's Response: If the use of se-creatinine groups yielded as valid and precise information regarding the prognostic value of renal function as eGFR groups, this approach would be easier. The cut-off values of se-creatinine groups were chosen on entirely empirical grounds. With a long period of follow-up, eGFR estimated by the Cockcroft-Gault formula showed similar results as the MDRD method .

Regarding the choice of method to the estimation of eGFR, we added the following text to the discussion:

Current manuscript (page 10, lines 18-23): “Of the several reliable formulas incorporating clinical variables, we used the MDRD formula, which is the best validated which has previously been used in 2 large studies. However, a study by Szummers showed that Cockcroft-Gault formula was better than the MDRD equation at predicting mortality after a MI. This was mainly explained by differences in the coefficients and variables included in the eGFR equations, and less to differences in various subgroups of patients.”

4) Most future readers of this study will not be familiar with wall motion index – it would have been better to use ejection fraction. At least the readers should be informed that wall-motion index #1.2 corresponds to an ejection fraction #35%.

Author's Response: We have added the following text to the results section:

Current manuscript (page 5, lines 13-15): “Wall motion index multiplied by 30 approximates left ventricular ejection fraction, hence a wall-motion index of 1.2 corresponds to an ejection fraction of 35 %”.

Minor issues not for publication

Abstract
- Results, 2nd sentence; put “in” after “(confidence interval (CI) 1,56 – 1,91)”

Author's Response: This has been corrected.

Discussion
- Third paragraph: “worsened” should be “worsen” and in the same sentence, put “of” between “cause” and “the”.
Author's Response: This has been corrected.

- Sixth paragraph, limitation section should be moved to the end of the Discussion section under the subheading “Limitation”

Author's Response: We have moved the section and included a subheading as requested.

- Last paragraph: all those references refer to heart failure/left ventricular dysfunction studies. It would be suitable to include some studies base on more pure ACS cohorts, such as by Santopinto, Fox, Al Suwaidi or Szummer.

Author's Response: The study by Al Suwaidi et al. are already mentioned in the discussion.

We have included studies by Santopinto, Fox and Szummer in the discussion and added the following text:

Current manuscript (page 13, lines 1-9): “The significance of creatinine clearance at the time of hospital admission was examined using data from the global registry of acute coronary events (GRACE) comprising 11 774 patients hospitalized with ACS. The results showed that in comparison with patients with normal or minimally impaired renal function, patients with moderate renal dysfunction were twice as likely to die and those with severe renal dysfunction almost four times more likely to die after adjustment for other potentially confounding variables. The risk of major bleeding episodes increased as renal function worsened”.

Current manuscript (page 13, lines 9-12): “Data from GRACE also showed that initial serum creatinine concentration was among the nine factors that independently predicted death and the combined end point of death and myocardial infarction in the period from admission to six months after discharge”.

Current manuscript (page 12, lines 12-15): “An observational study of 57477 consecutive MI patients showed that declining GFR estimated by the MDRD formula was associated with an increased rate of complications and a higher rate of in-hospital mortality”.

Current manuscript (page 15, lines 6-10): “It has previously been shown that early invasive therapy defined as revascularization within 14 days of admission was associated with greater 1-year survival in patients with non-ST-elevation myocardial infarction and mild-to-moderate renal insufficiency, but the benefit declined with lower renal function”.

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