Reviewer's report

Title: Renal function at the time of a myocardial infarction maintains prognostic value for 16 years

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Study summary
Renal function at the time of a myocardial infarction maintains prognostic value for 16 years

The population consisted of a mixed MI population from historical times when we did not subdivide acute coronary syndromes into STEMI and NSTEMI patients. The patients were all screened for inclusion into the TRACE study, n=6676. 23 patients lacked information about renal function and were not included in further analyses. 24-50% of the patients got thrombolysis, the lowest rate in the highest CKD stage. 78% of the patients died during follow-up, 17 years. 44% had renal insufficiency, i.e. eGFR<60 ml/min according to one single s-creatinine analysis on arrival, MDRD formula used. CKD stages less than 2 were independently associated with poor long term outcome after adjusting for age, gender, thrombolysis, diabetes, angina, hypertension, heart failure and left ventricular function.

Several studies from randomized controlled trials as well as from observational registries are published during the last decade regarding the prognostic impact of mild to moderate renal insufficiency (eGFR<60 ml/min) after MI, such as by Fox et al, Al Suwaidi et al, Szummer et al, Santopinto et al and by Anavekar et al. Anyway, I agree with the authors that the impact of different stages of CKD on real long term prognosis (more than 1 year) after MI is less firmly evaluated.

Thus the study is of much interest but there are several issues to be addressed in the study to make it more understandable for the readers. I recommend it should be published after major revisions.

Comments

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.

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.

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 seems 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?

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 eGFR group 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).

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

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.

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 statisticistical 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.

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 variable and use stage 1 or 1-2 combined (or above 75ml/min as the authors did) as reference group.

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?

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.

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 umol/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?

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 Cockgroft Gault
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.

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%.

Minor issues not for publication

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

Discussion
- Third paragraph: “worsened” should be “worsen” and in the same sentence, put “of” between “cause” and “the”.
- Sixth paragraph, limitation section should be moved to the end of the Discussion section under the subheading “Limitation”
- Last paragraph: all those references refer to heart failure/left ventricular dysfunction studies. It would be suitable to include some studies based on more pure ACS cohorts, such as by Santopinto, Fox, Al Suwaidi or Szummer.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
I declare that I have no competing interests