

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Gender difference in the prognostic value of estimated glomerular filtration rate at admission in ST-segment elevation myocardial infarction; a prospective cohort study.
AUTHORS	Peter Damman, Wouter J Kikkert, Pier Woudstra, Wichert J Kuijt, Maik Grundeken, Ralf E Harskamp, Jan Baan, Marije M Vis, Jose PS Henriques, Jan J Piek, Jan P van Straalen, Johan Fischer, Jan G P Tijssen and Robbert J de Winter

VERSION 1 - REVIEW

REVIEWER	<p>Sofia Sederholm Lawesson, M.D. Department of Medical and Health Sciences, Division of Cardiovascular Medicine, Linköping University Hospital, SE-581 85 Linköping, Sweden</p> <p>I have no conflict of interest more than that I am the corresponding author of the Swedish paper that the authors of the current paper refer to in the introduction and discussion.</p>
REVIEW RETURNED	14/09/2011

THE STUDY	<p>The objective is not clearly stated in the introduction. Is the interaction between sex and RI regarding long term outcome the main objective? The relation between gender and prevalence of RI is not evaluated in the paper.</p> <p>The patients are probably representative to PPCI patients but it would have been better to include all consecutive STEMI patients during the study period. According to the method section 2217 patients were included (all STEMI patients who underwent PPCI) but according to the result section only 1970 patients were included. A flow chart of numbers potentially and confirmed eligible and finally included and reasons for non-participation should be added for clarification.</p> <p>The key reference - the Swedish paper that the author compare their results with - is not in the reference list. The reference nr 3 should be replaced with the paper "Gender difference in prevalence and prognostic impact of renal insufficiency in patients with ST-elevation myocardial infarction treated with primary percutaneous coronary intervention" by Lawesson et al. The other references are few but seem adequate although a reference regarding the Cockcroft Gault formula and the authors did not explain the formula to the readers.</p>
RESULTS & CONCLUSIONS	<p>There are some flaws in the tables and the figures and also some findings needing explanation/discussion:</p> <p>Table 1</p>

	<p>Is the difference in TnT level between RI and nonRI among males really statistically significant <0.001? The number is the same but with different IQR.</p> <p>The infarctions seem to be bigger/more severe according to the NTproBNP levels, angiographic findings and the rate of shock but not according to the TnT levels in RI patients. Could the authors discuss that and maybe add data from echocardiography regarding LV-function? Also, why is time to treatment longer in the RI patients?</p> <p>Table 1 contains a lot of information that is never discussed and could be either reduced or the findings could be further discussed in the Discussion part.</p> <p>Table 2 The third multivariable model regarding 30-day and long term outcome: how is eGFR incorporated in the model? Over 60 = HR 1.00 (ref)? Please clarify!</p> <p>Figure 1 The labels in Figure 1 must be wrong - I guess the red curves (60.3 and 61.7% mortality) represent CKD stage 3B-5 whereas the blue curves (8 and 10.7% mortality) represent CKD stage 1-2.</p> <p>The No. at risk in women with eGFR ≥ 60 are not the same in Figure 1 and Figure 2 (410 and 420 respectively).</p> <p>The No. at risk in the end of the study indicates either a much higher mortality than in the figures or much loss to follow-up (see also figure 2). Please clarify!</p> <p>Figure 2 This figure could be omitted – it does not contribute with more information than Figure 1, also log rank tests comparing the genders are missing. The No. at risk in the end of the study indicates either a much higher mortality than in the figures or much loss to follow-up (87 living women with RI after 3 years out of 410 from the beginning=78% dead). Please clarify!</p> <p>Discussion According to this study men have three times higher hazard of dying compared to women after adjustments according to the study which is the opposite finding as compared to the Swedish study that the current study refer to. These contradictory findings needs to be more discussed more thoroughly.</p> <ol style="list-style-type: none"> 1) the two studies used different formulas (MDRD vs CG) - how did that affect the results 2) Is the difference in “all over co-morbidity” much more pronounced between men with and without RI than in women with and without RI? 3) The confidence intervals are also very broad and the results must be interpreted with precaution. 4) The absolute figures on overall mortality in 30 day and in long term mortality in RI and non RI male and female patients also ought to be added to the manuscript. 5) Is it correct to incorporate weight in the model as CrCl estimated by CG is a function of age, sex, weight and creatinine? Age is a very important prognostic factor regarding mortality post-MI and must be adjusted for but as weight has not the same impact on mortality, I suggest that the authors omit weight from their analyses. Does that
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	affect the results? 6) RI is much more prevalent in women than in men among STEMI patient which may have affected the results (in the current study 9% of men compared to 25% of women had RI - in the Swedish study the prevalence was much higher in both men and women based on the MDRD formula).
REPORTING & ETHICS	A section about ethics is lacking. Was the study approved by an ethic committee?

REVIEWER	Inga Soveri, Uppsala University
REVIEW RETURNED	18/11/2011

THE STUDY	estimation of GFR was not optimal errors in the abstract (such as gender distribution of the patients) incorrectly cited reference (3).
RESULTS & CONCLUSIONS	Figure 1 contradicts with the text. incorrectly cited reference
REPORTING & ETHICS	Ethics not addressed
GENERAL COMMENTS	Review. BMJ Open Damman P, et al. "Gender difference in the prognostic value of eGFR at admission in ST-segment elevation myocardial infarction, a prospective cohort study. The authors show that eGFR has prognostic significance for mortality after ST-elevation myocardial infarction in both male and female patients. Comments: I support publishing of confirmatory studies. The authors of this manuscript have access to data that gives them the potential to produce a paper of good quality. However, the submitted manuscript is not well written. 1. There are several mistakes in the abstract already (Design, Patients) and the Objective and Main Outcome Measure sections need to be re-written. 2. The authors need to check their references. For example, the authors refer [3] to the study by Lawesson, et al (Heart 2010), that studied STEMI patients below 46 years of age. Only 2.1% (not 67% as written in the manuscript) of the women in that study had CKD, etc... 3. In Figure 1, the authors present higher mortality in the better renal function group?! 4. GFR was estimated by Cockcroft-Gault equation. The formula gives, strictly, creatinine clearance (mL/min). The authors need to distinguish between absolute and relative (BSA-adjusted) GFR in different studies. 5. Ethics committee approval of the study needs to be mentioned.

	<p>Recommendations for improvement:</p> <p>The strength of the study is, that the authors had access to enzymatic creatinine assay. Many earlier studies have not had access to enzymatic creatinine assay. I would recommend to consult the laboratory about whether the assay used was IDMS-traceable. If so, a MDRD or CKD-EPI equation for GFR estimation could be used when elaborating the manuscript.</p>
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VERSION 1 – AUTHOR RESPONSE

Bmjopen-2011-000322

Gender difference in the prognostic value of estimated glomerular filtration rate at admission in ST-segment elevation myocardial infarction, a prospective cohort study

Comments of the reviewers.

Reviewer 1.

We thank reviewer 1 (Dr. Lawesson) for the careful assessment of our manuscript.

Reviewer 1, comment 1

The objective is not clearly stated in the introduction. Is the interaction between sex and RI regarding long term outcome the main objective? The relation between gender and prevalence of RI is not evaluated in the paper.

Reply

In the introduction we state *“This counterintuitive finding deserves confirmation. In the current manuscript, we evaluate the relation between gender and renal function in STEMI patients undergoing PPCI in a large single centre in the Netherlands.”*

In the first sentence, we are referring to the manuscript of Lawesson et al., in which a gender difference was described regarding the prognostic value of renal function. Our objective was to confirm this gender difference. We changed the second sentence in order to better reflect this objective.

Changes to the manuscript

We changed *“In the current manuscript, we evaluate the relation between gender and renal function in STEMI patients undergoing PPCI in a large single centre in the Netherlands.”* to *“For the current manuscript, the main objective was to evaluate gender differences in the relation between renal function and outcomes in STEMI patients undergoing PPCI in a large single centre in the Netherlands.”* on page 4 of the manuscript.

Reviewer 1, comment 2

The patients are probably representative to PPCI patients but it would have been better to include all consecutive STEMI patients during the study period. According to the method section 2217 patients were included (all STEMI patients who underwent PPCI) but according to the result section only 1970

patients were included. A flow chart of numbers potentially and confirmed eligible and finally included and reasons for non-participation should be added for clarification.

Reply

We agree with the reviewer that this needs clarification. In the first sentence of the results we state “*We included 1970 patients with a measured eGFR in our current study.*” Thus all patients excluded were patients with missing eGFR values. However, this will probably not be due to a selection bias, because kreatinin was routinely measured prior to PPCI.

Changes to the manuscript

We added the following sentence to page 5 of the methods section: *Patients in whom we were not able to calculate an eGFR were excluded.*

Reviewer 1, comment 3

The key reference - the Swedish paper that the author compare their results with - is not in the reference list. The reference nr 3 should be replaced with the paper "Gender difference in prevalence and prognostic impact of renal insufficiency in patients with ST-elevation myocardial infarction treated with primary percutaneous coronary intervention" by Lawesson et al.

Reply

We apologize for the error and changed the reference.

Changes to the manuscript

Changed reference number 3.

Reviewer 1, comment 4

“...a reference regarding the Cockcroft Gault formula...”

Reply

We added a reference regarding the Cockcroft Gault formula.

Changes to the manuscript

We added a reference regarding the Cockcroft Gault formula.

Reviewer 1, comment 5

Table 1

Is the difference in TnT level between RI and nonRI among males really statistically significant <0.001? The number is the same but with different IQR.

The infarctions seem to be bigger/more severe according to the NTproBNP levels, angiographic findings and the rate of shock but not according to the TnT levels in RI patients. Could the authors discuss that and maybe add data from echocardiography regarding LV-function? Also, why is time to treatment longer in the RI patients?

Reply

It is true that the difference is significant. Despite identical median TnT values among male patients with and without renal impairment, the interquartile range (0.09 – 0.59 in male patients with renal

impairment versus 0.04 – 0.20 in male patients without renal impairment) show that the highest quartile in the male patients with renal impairment consist of larger infarctions than the highest quartile within the male patients without renal impairment, As already mentioned by the reviewer, this is supported by the NTproBNP levels, the angiographic findings and the rate of shock.

We do not have routine echocardiography data available in our centre, thus we are not able to present this data.

We hypothesize that the longer time to treatment in the patients with renal impairment might be influenced by the higher age and higher diabetes rates in this patients. Higher age and diabetes are factors associated with an increased time to treatment. Finally, it might be a spurious finding.

Changes to the manuscript

None.

Reviewer 1, comment 6

Table 1 contains a lot of information that is never discussed and could be either reduced or the findings could be further discussed in the Discussion part.

Reply

We agree with the reviewer that Table 1 might be to extensive. Because we believe that the for the completeness of the presentation both the male and female patients with/without renal impairment should be shown, we decided to delete some of the baseline characteristics that were not used in the multivariable analyses.

Changes to the manuscript

Removed multiple variables from Table 1 that were not used in the multivariable analyses.

Reviewer 1, comment 7

Table 2

The third multivariable model regarding 30-day and long term outcome: how is eGFR incorporated in the model? Over 60 = HR 1.00 (ref)? Please clarify!

Reply

The reviewer is correct, for all Cox regression models, an eGFR of 60 or higher is used as the reference category (with an HR of 1.00). In order to clarify, we added this below Table 2.

Changes to the manuscript

Added the following sentence below Table 2. : *“For all Cox models. the reference category for the eGFR variable is eGFR ≥60 ml/min.”*

Reviewer 1, comment 8

Figure 1

The labels in Figure 1 must be wrong - I guess the red curves (60.3 and 61.7% mortality) represent CKD stage 3B-5 whereas the blue curves (8 and 10.7% mortality) represent CKD stage 1-2.

Reply

We thank the reviewer for noticing this error.

Changes to the manuscript

Changed the labels in figure 1.

Reviewer 1, comment 9

The No. at risk in women with eGFR ≥ 60 are not the same in Figure 1 and Figure 2 (410 and 420 respectively).

Reply

We thank the reviewer for noticing this error.

Changes to the manuscript

The numbers at risk in Figure 1 were correct. Because Figure 2 is omitted from the final version of the manuscript, we did not have to change the numbers at risk under Figure 2.

Reviewer 1, comment 10

The No. at risk in the end of the study indicates either a much higher mortality than in the figures or much loss to follow-up (see also figure 2). Please clarify!

Reply

The numbers at risk at the end of the study represent patients who were lost to follow-up or for whom the last known date of follow-up is shorter than the end of follow-up. If these patients would have died, we would identify them in the Dutch national population registry,

Regarding the loss to follow-up, it is comparable over all strata, and is accounted for in the Kaplan-Meier estimates. If it represented mortality, the Kaplan-Meier estimates were much higher,

Changes to the manuscript

None.

Reviewer 1, comment 11

Figure 2

This figure could be omitted – it does not contribute with more information than Figure 1, also log rank tests comparing the genders are missing. The No. at risk in the end of the study indicates either a much higher mortality than in the figures or much loss to follow-up (87 living women with RI after 3 years out of 410 from the beginning=78% dead). Please clarify!

Reply

We agree that Figure 2 could be omitted and removed Figure 2 from the manuscript. As indicated with comment 10, the low patient numbers at risk do not indicate a very high mortality but a loss to follow-up.

Changes to the manuscript

Removed Figure 2.

Reviewer 1, comment 12

Discussion

According to this study men have three times higher hazard of dying compared to women after adjustments according to the study which is the opposite finding as compared to the Swedish study that the current study refer to. These contradictory findings needs to be more discussed more thoroughly.

- 1) the two studies used different formulas (MDRD vs CG) - how did that affect the results
- 2) Is the difference in "all over co-morbidity" much more pronounced between men with and without RI than in women with and without RI?
- 3) The confidence intervals are also very broad and the results must be interpreted with precaution.
- 4) The absolute figures on overall mortality in 30 day and in long term mortality in RI and non RI male and female patients also ought to be added to the manuscript.
- 5) Is it correct to incorporate weight in the model as CrCl estimated by CG is a function of age, sex, weight and creatinine? Age is a very important prognostic factor regarding mortality post-MI and must be adjusted for but as weight has not the same impact on mortality, I suggest that the authors omit weight from their analyses. Does that affect the results?
- 6) RI is much more prevalent in women than in men among STEMI patient which may have affected the results (in the current study 9% of men compared to 25% of women had RI - in the Swedish study the prevalence was much higher in both men and women based on the MDRD formula).

Reply

We agree that the finding should be discussed more thoroughly, and incorporated some of the suggestions of the reviewer.

- 1) The different formulas probably affect a small part of the results. If we (incorrectly in our population assume that all patients are non-black) calculate the eGFR again using the MDRD the following multivariable results are observed

MDRD male eGFR under 60 ml/min versus above : HR 7.10 (95%CI: 4.50-11.21)

MDRD female eGFR under 60 ml/min versus above : HR 2.75 (95%CI: 1.60-4.70)

CG male eGFR under 60 ml/min versus above : HR 11.58 (95%CI: 5.39-24.91)

CG female eGFR under 60 ml/min versus above : HR 3.41 (95%CI: 1.38-8.44)

Thus, we observe the same quantitative different, but prognostic value of renal dysfunction in both male and female patients using the MDRD or Cockcroft-Gault equations.

- 2) We agree with the reviewer that this might be a contributing factor. As Table 1 (Baseline characteristics) generally indicates, male patients with an eGFR of 60 ml/min or above have a lower frequency of risk factors, a less extensive history, and lower biomarkers than the female patients with an eGFR of 60 ml/min or above.

We added this to the discussion section of the manuscript.

3) We agree that it might be a spurious finding due to small patient numbers, and added this to the discussion section on page 12.

4) The long-term all-cause death rates were already according to renal (dys)function were already presented in Figure 2, and we agreed with the reviewer to remove this figure. Results at 30-days and long-term follow-up were consistent, so we hope the reviewer agrees to omit these extra Figures in order to make the manuscript easier interpretable.

5) We incorporated these factors as these were established risk factors for mortality and are all summarized in the frequently used TIMI risk score. We agree with the reviewer that it might be an 'over-correction', and repeated the multivariable models excluding age and body weight. Comparable results were observed without these two risk factors.

6) This might have led to a difference in study populations, and we added this to the discussion section.

Changes to the manuscript

We added the following sentence to the discussion on page 12 "*Other possible explanations might be that the male patients with an eGFR > 60 ml/min generally had a more favourable baseline risk profile compared to the female patients with an eGFR > 60 ml/min.*"

We added the following sentence to the discussion section on page 12 "*Finally, the quantitative difference might be a spurious finding as indicated by the broad confidence intervals.*"

We added the following sentence to the discussion section on page 12 "*One notable exception might be the higher percentage of female patients with renal dysfunction in the Swedish study population.*"

Reviewer 1, comment 13

A section about ethics is lacking. Was the study approved by an ethic committee?

Reply

The study was approved by the institutional ethical review committee.

Changes to the manuscript

We have added the following sentence to the methods section on page 6: "*The study was approved by the institutional ethical review committee.*"

Bmjopen-2011-000322

Gender difference in the prognostic value of estimated glomerular filtration rate at admission in ST-segment elevation myocardial infarction, a prospective cohort study

Comments of the reviewers.

Reviewer 2.

We thank reviewer 2 (Dr. Soveri) for the careful assessment of our manuscript.

Reviewer 2, comment 1

There are several mistakes in the abstract already (Design, Patients) and the Objective and Main Outcome Measure sections need to be re-written.

Reply

We apologize for the mistakes, and have rewritten parts of the abstract, objective and main outcome measure sections.

Changes to the manuscript

We adjusted the abstract.

Reviewer 2, comment 2

The authors need to check their references.

For example, the authors refer [3] to the study by Lawesson, et al (Heart 2010), that studied STEMI patients below 46 years of age. Only 2.1% (not 67% as written in the manuscript) of the women in that study had CKD, etc.

Reply

We apologize for the mistakes. However, Lawesson et al do state that 67% of the female patients had renal insufficiency.

Changes to the manuscript

- 1) Replaced reference 3 with the correct study.

Reviewer 2, comment 3

In Figure 1, the authors present higher mortality in the better renal function group?!

Reply

We thank the reviewer for noticing this error.

Changes to the manuscript

Changed the labels in figure 1.

Reviewer 2, comment 4

GFR was estimated by Cockcroft-Gault equation. The formula gives, strictly, creatinine clearance (mL/min). The authors need to distinguish between absolute and relative (BSA-adjusted) GFR in different studies.

Reply

As the reviewer correctly suggests, different formulas were used for the estimation of GFR in the current and Swedish studies, The different formulas probably affect a small part of the results. If we (incorrectly in our population assume that all patients are non-black) calculate the eGFR again using the MDRD the following multivariable results are observed

MDRD male eGFR under 60 ml/min versus above : HR 7.10 (95%CI: 4.50-11.21)

MDRD female eGFR under 60 ml/min versus above : HR 2.75 (95%CI: 1.60-4.70)

CG male eGFR under 60 ml/min versus above : HR 11.58 (95%CI: 5.39-24.91)

CG female eGFR under 60 ml/min versus above : HR 3.41 (95%CI: 1.38-8.44)

Thus, we observe the same quantitative different, but prognostic value of renal dysfunction in both male and female patients using the MDRD or Cockcroft-Gault equations.

Changes to the manuscript

None

Reviewer 2, comment 5

Ethics committee approval of the study needs to be mentioned.

Reply

The study was approved by the institutional ethical review committee.

Changes to the manuscript

We have added the following sentence to the methods section on page 6: *“The study was approved by the institutional ethical review committee.”*

Reviewer 2, recommendations for improvement:

The strength of the study is, that the authors had access to enzymatic creatinine assay. Many earlier studies have not had access to enzymatic creatinine assay. I would recommend to consult the laboratory about whether the assay used was IDMS-traceable. If so, a MDRD or CKD-EPI equation for GFR estimation could be used when elaborating the manuscript.

Reply:

Unfortunately we did not have access to these data.

VERSION 2 – REVIEW

REVIEWER	Inga Soveri MD, PhD Department of Medical Sciences, Uppsala University Sweden
REVIEW RETURNED	01/01/2012

RESULTS & CONCLUSIONS	The manuscript has been improved, but still difficult to read due to mistakes. The authors discuss previous studies, but not all relevant aspects, such as different GFR-estimation.
GENERAL COMMENTS	The manuscript has undergone improvement and the reference list and Figure 1 have been corrected. However, there are mistakes remaining in the abstract and the main body, making the paper difficult to read. Loss to follow-up needs to be explained to the reader. The impact of different GFR estimation-methods in comparable studies definitely needs to be discussed.

VERSION 2 – AUTHOR RESPONSE

Bmjopen-2011-000322

Gender difference in the prognostic value of estimated glomerular filtration rate at admission in ST-segment elevation myocardial infarction, a prospective cohort study

Comments of the reviewers.

Reviewer 2.

We thank reviewer 2 (Dr. Soveri) for the careful assessment of our revised manuscript.

Reviewer 2, comment 1

The manuscript has been improved, but still difficult to read due to mistakes.

Reply

We thoroughly went through the manuscript and corrected mistakes where possible.

Changes to the manuscript

We adjusted the abstract and main body of the text where possible.

Reviewer 2, comment 2

The authors discuss previous studies, but not all relevant aspects, such as different GFR-estimation.

Reply

We agree, and added a section on the different eGFR estimations.

Changes to the manuscript

We added the following section to page 13 of the manuscript.

Reviewer 2, comment 3

Loss to follow-up needs to be explained to the reader.

Reply

We agree and added this to the results.

Changes to the manuscript

We added the following sentence to the results on page 9.