PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Time trends in STEMI - improved treatment and outcome but still a gender gap: A prospective, observational cohort study from the SWEDEHEART register
AUTHORS	Sofia Sederholm Lawesson, Joakim Alfredsson, Mats Fredrikson and Eva Swahn

VERSION 1 - REVIEW

REVIEWER	Raffaele Bugiardini, MD FESC FAHA, FACC, Full Professor of Cardiology Department of Internal Medicine Cardiology Section University of Bologna (Italy) Ospedale S.Orsola via Massarenti 9 bologna competing interests: none
REVIEW RETURNED	30/12/2011

RESULTS & CONCLUSIONS	1.- Data on 1 year mortality was not part of a prospective FU but rather obtained from a National registry. Co-morbidities were obtained from another registry. 2.- Among patients treated with reperfusion therapy, 9% were treated with primary PCI in the early period compared to 68% in the late period. This is clear in the text but should be clarified (as compared with all patients not only among those receiving reperfusion) in the abstract and table where remains difficult to follow. 3.- Results of the multivariate models are rather confusing. They are described in the statistical analysis but then in the results the model and the final results remain unclear. I would suggest to present crude risk estimates and then adjusted risk ratios (or HR) with 95%CI, according to all selected models for all main outcome measures. Perhaps a figure summarizing all this information (main study findings) would be illustrative. 4.- The figures with the global trends belong to the results section (data) rather than to the discussion. Trends in these figures are not easy to follow. Actually, they do not appear to show divergent patterns over time among genders. 5.- The fact that no change in the second period was noted in the rate of reperfusion therapy in women should be emphasized. This may be a reason for the final results, in addition to the reduced use of EBM medications. 6.- Data on potential gender bias and final results in the specific

	cohort of patients receiving just primary PCI (second period) would be of major interest. In addition, references 16-19 specifically addressed gender bias in STEMI patients undergoing primary PCI. These results should be discussed in further detail and compared with the results of the present study. 7.- The fact that the gender gap seems to be even more pronounced in the current era is of major interest. However, a potential explanation to account for this finding (in contradistinction with the original hypothesis) should be advanced to the readers.

REVIEWER	Hani Jneid, MD, FACC, FAHA, FSCAI Assistant Professor of Medicine Baylor College of Medicine Houston, Tx - USA I have no competing interests
REVIEW RETURNED	17/01/2012

THE STUDY	Advise enhance the writing some of the sections and make them clearer - Overall, I find the manuscript very interesting – The analyses are well conducted and the findings interesting and relevant to BMJ readers and the general medical community - I advise accepting it with minor modifications - I will be happy to provide an authoritative editorial on the topic if deemed necessary -
GENERAL COMMENTS	1. Please, substitute the term gender with the more biological term 'Sex' 2. The result section in the abstract is quite unclear and needs to be re-written – I advise to specify the important EBMs rather than lump them into one category- 3. Are these merged database administrative or research databases – please, clarify and indicate differences and limitations – 4. Was the appropriateness of the evidence-based therapies at discharge (platelet inhibitors, beta-blockers, ACE-inhibitors/ARBs and statins) assessed? For example, an STEMI with AKI or CKD (with Cr 4.0) might have been appropriately denied ACE-I/ARB rx – 5. I advise to report EBMs as their separate medications and not include them together, given inability to ascertain appropriateness of these medications and sex disparity across different medications - 6. Do you have data on timeliness of reperfusion (door-to-balloon and door-to-nnedle)? Please, indicate as study limitation – 7. Did you adjust for the cluster effect by hospital? If not, please discuss and indicate as potential limitation – 8. STEMI patients undergoing coronary angiography were 66% and 82% among women and men in the 2004 – 2006 period, which seems to me a bit low for this patient population in the current era – please, can you comment on this and on the generalizability of your findings to other healthcare systems –

	9. Advise to have the tables and figures at the end of the manuscript – 10. In the final Conclusion section, I advise to focus on the persistent mortality gap among women and men presenting with STEMI -

VERSION 1 – AUTHOR RESPONSE

Response to reviewer Raffaele Bugiardini, MD FESC, FAHA, FACC,
Full Professor of Cardiology
Department of Internal Medicine, Cardiology Section, University of Bologna (Italy), Ospedale S.Orsola via Massarenti 9 Bologna

The reviewer suggests:
- The results paragraph is confusing, authors should comment on demographics, cardiovascular risk factors, then baseline medications between the two periods and between men and women.
Answer:
There were differences in between the time periods regarding CVD risk factors and medications, as shown in Table I. We have now stressed the most important ones also in text.

The reviewer suggests:
-To use an ischemic risk score (TIMI Score for STEMI or GRACE score ...).
Answer:
We have chosen to not use the TIMI risk score for STEMI as too many variables included in the score are missing in the register being not compulsory (weight, heart rate, blood pressure). All of the remaining variables are incorporated in our multivariable analyses.

The reviewer suggests:
- troponin or CPK peak values would be important to know as women underwent less frequently reperfusion
Answer:
Regarding myocardial biomarkers, it is an interesting question. We have done some analyses and find a significant gender difference regarding CKMB, and TnT (max values) in both periods. Anyhow the shift from CKMB to troponins during this time period has not been done simultaneously in the different hospitals and some have chosen TnT and others TnI (in addition TnI was analysed with several different methods) which makes the interpretation of the data very difficult. In addition, in STEMI patients the biomarkers have little impact on how to treat the patients. Thus we think we cannot add this in the article.

The reviewer suggests:
1.- Data on 1 year mortality was not part of a prospective FU but rather obtained from a National registry. Co-morbidities were obtained from another registry.
Answer:
Regarding the endpoint 1-year (all-cause) mortality, information is taken from the National Cause of Death Register and this register is merged with RIKS-HIA/SWEDEHEART. In Sweden each person has a unique personal identification code and thus nobody is lost to follow-up, i.e. all deaths are registered. Information of the different registries and the merging process is now clarified in the method part.

The reviewer suggests:
2.- Among patients treated with reperfusion therapy, 9% were treated with primary PCI in the early period compared to 68% in the late period. This is clear in the text but should be clarified (as

compared with all patients not only among those receiving reperfusion) in the abstract and table where remains difficult to follow.
Answer:
To clarify: Among all patients in the early group, 7.0% of men and 4.5% of women were treated with primary PCI. Among all patients treated with reperfusion therapy, 9% were treated with PPCI. Among all patients in the late group, 52.2% of men and 40.7% of women were treated with PPCI. Among patients treated with reperfusion therapy, 68% were treated with PPCI. This is now clarified in the abstract and added in the table.

The reviewer suggests:
3.- Results of the multivariate models are rather confusing. They are described in the statistical analysis but then in the results the model and the final results remain unclear. I would suggest to present crude risk estimates and then adjusted risk ratios (or HR) with 95% CI, according to all selected models for all main outcome measures. Perhaps a figure summarizing all this information (main study findings) would be illustrative.
Answer:
As suggested by the reviewer, crude risk estimates and multivariable adjusted odds ratios/hazard ratios with confidence intervals are presented for the outcome measures and in addition age adjusted data. The details are presented in the statistic part and visualised in Forest plots, the odds/hazard ratios (with 95% CI) are also given in the Supplementary Table.
The reviewer suggests:
4.- The figures with the global trends belong to the results section (data) rather than to the discussion. Trends in these figures are not easy to follow. Actually, they do not appear to show divergent patterns over time among genders
Answer:
In the manuscript there is only one figure on global trends, placed in the method section.

The reviewer suggests:
5.- The fact that no change in the second period was noted in the rate of reperfusion therapy in women should be emphasized. This may be a reason for the final results, in addition to the reduced use of EBM medications
Answer:
This is discussed and emphasised in the discussion part.

The reviewer suggests:
6.- Data on potential gender bias and final results in the specific cohort of patients receiving just primary PCI (second period) would be of major interest. In addition, references 16-19 specifically addressed gender bias in STEMI patients undergoing primary PCI. These results should be discussed in further detail and compared with the results of the present study.
Answer:
Just to clarify; our late group did not include only primary PCI patients but included all STEMI patients. In total (Table I) 52.2% of the men and 40.7% of the women underwent PPCI in the late group. The finding from older primary PCI studies focusing on the gender aspect such as ref 7-10 (Antoniucci, De Luca and Motovska) laid ground to our hypothesis that the gender gap in reperfusion therapy as well as mortality would have diminished with the reperfusion strategy shift (see introduction). References 16-19 (Champney; Eagle, Reynolds and Keeley) do not address gender bias in STEMI patients undergoing primary PCI. In the discussion part, from the primary PCI era we compared our result with two more recent primary PCI studies focusing on the gender aspect; (Benamer and Sadowski) ref 28 and 29.

The reviewer suggests:
7.- The fact that the gender gap seems to be even more pronounced in the current era is of major

interest. However, a potential explanation to account for this finding (in contradistinction with the original hypothesis) should be advanced to the readers.
Answer:
We have elaborated upon this issue in the discussion part as follows:

“Thus, our hypothesis was that the gender gap in reperfusion therapy would diminish after the shift to a reperfusion strategy that could be more advantageous to women. This hypothesis was not confirmed. The rate of reperfusion in men increased from 70.9% to 75.3% whereas the increase in women was very modest, 63.1% to 63.6%. The reason for the finding is for us unclear. Mean age was the same in the two periods and women had 30 min longer symptom-to-door time in both periods. One possible reason could be higher prevalence of normal coronary arteries in women, which is shown before although mainly in NSTEACS and
mixed ACS populations.[23] In our study, during the early period we had coronary angiography findings from few patients (56% of the 3514 patients that underwent coronary angiography). In the late period we had findings on 97 % of the 11 002 examined patients showing that 3% of men and 7 % of women had nonobstructive coronary artery disease. Thus, normal coronary arteries can hardly explain the gap in reperfusion therapy in the early period when fibrinolytics was dominating and angiography seldom performed. In the late period it could account for a small part of the difference in use of primary PCI although it does not explain the gender gap in use of coronary angiography, which also increased between the two time periods.
……..

We cannot fully explain this gender gap in management. Maybe a fear of doing harm because of the wellknown higher risk of bleeding in women [26] or reports from patients of previous or current adverse effects are reasons for the bias. It has been shown in previous studies that women report side effects more often than men, especially if the same dosages are used. [27] Finally, we could speculate that doctors tend to adapt to new treatment modalities and new guidelines faster in men than in women, especially in older cohorts. We did some subgroup analyses of different age groups (not included in the manuscript) where we found the
treatment bias clearest in the oldest cohort.”

Response to reviewer Hani Jneid, MD, FACC, FAHA, FSCAI Assistant Professor of Medicine Baylor College of Medicine Houston, Tx - USA

The reviewer suggests:
1. Please, substitute the term gender with the more biological term ‘Sex’
Answer:
We have thoroughly discussed the terms "sex" and "gender" previously, as it is most often a delicate matter which of the terms that ought to be used. In this particular manuscript we handle the issue whether men and women have the same chance to get evidence based management in the STEMI setting, and how prognosis is affected. We are not sure that only biological reasons explain the difference we found, why we used the word "gender". As biological reasons also affect the difference between men and women as regards management and outcome (age, CKD, diabetes prevalence etc), we can of course change gender to sex if there is an agreement from the Editorial Office upon this matter.

The reviewer suggests
2. The result section in the abstract is quite unclear and needs to be re-written – I advise to specify the important EBMs rather than lump them into one category
Answer:
We have now rewritten the abstract accordingly, especially the result part. We have explained the

term EBM as well as specified the important evidence based cardiovascular drugs at discharge.

The reviewer suggests:
3.Are these merged database administrative or research databases – please, clarify and indicate differences and limitations
Answer:
The method part is now expanded with more information about the separate. SWEDEHEART/RIKS-HIA, as a national quality register, has been used extensively for research purposes. The national administrative registers (the National Cause of Death Register and the National Patient Register) were used to gather data on vital status and on co-morbidity. Information on previous cardiovascular diseases was obtained from both SWEDEHEART and the Patient National Register, whereas information on non-cardiovascular diseases was obtained from only the National Patient Register. A limitation of the latter is that diagnoses from e.g. general practitioners will not be registered as it only covers hospital diagnoses coded in the patient files. In SWEDEHEART the nurse and physician actively register more than 100 variables about the patient, and the patient is actively asked about his/her previous cardiovascular diagnoses etc.

The reviewer suggests:
4.Was the appropriateness of the evidence-based therapies at discharge (platelet inhibitors, beta-blockers, ACE-inhibitors/ARBs and statins) assessed? For example, an STEMI with AKI or CKD (with Cr 4.0) might have been appropriately denied ACE-I/ARB rx
Answer:
Contraindications to and/or adverse effects caused by specific drugs are not registered in SWEDEHEART (see limitation part in discussion, now somewhat expanded).

The reviewer suggests:
5.I advise to report EBMs as their separate medications and not include them together, given inability to ascertain appropriateness of these medications and sex disparity across different medications
Answer:
We have to a large extent omitted the acronym EBM and clarified and report the evidence-based therapies as the separate medications

The reviewer suggests:
6.Do you have data on timeliness of reperfusion (door-to-balloon and door-to-nnedle)? Please, indicate as study limitation
Answer:
Yes, we have time-data. The best registered time-variable was symptom-to-door (CCU or cath lab) time, which was therefore used in the multivariable analyses as women have longer patient delay time compared to men (see Supplementary table). As regards the so called doctors delay time door-to-needle/balloon time is not registered for all patients probably because some arrive to ER first, others directly to CCU or to cath lab and some do get their reperfusion treatment already in the ambulance (fibrinolytics). On the other hand we have data on time from 1st ECG to needle/balloon for the majority of patients (this is very similar to time from first medical contact, which is now recommended to be used). We have thus added these results in the result part of the manuscript as well as in Table 1.

The reviewer suggests:
7.Did you adjust for the cluster effect by hospital? If not, please discuss and indicate as potential limitation
Answer:
No, we did not take the potential cluster effect by hospital into consideration, but we actually do not think this is a limitation as we used the whole population of Swedish STEMI patients (not a sample of

hospitals). To clarify; all Swedish hospitals (small, medium as well as high volume hospitals) deliver data to SWEDEHEART. In addition yearly open comparisons between the hospitals are reported from SWEDEHEART, with relatively small differences in EBM. Finally, our focus is gender differences. Anyhow, in the multivariable adjustments, type of hospital (interventional hospital or not) is included.

The reviewer suggests:
8.STEMI patients undergoing coronary angiography were 66% and 82% among women and men in the 2004 – 2006 period, which seems to me a bit low for this patient population in the current era – please, can you comment on this and on the generalizability of your findings to other healthcare systems

Answer:
Yes, these are the Swedish numbers for these two time periods from the national quality register SWEDEHEART including the national quality register for angiography/angioplasty. After the year 2006 (last year of registration in our manuscript) the use of angiography and primary PCI has continuously increased as well as the percentage of STEMI patients receiving any kind of reperfusion therapy. According to the SWEDEHEART report from 2010, 88% of the STEMI patients underwent primary PCI year 2010.
In comparison with a report from the GRACE register (including a total of 113 hospitals located in 14 countries; Argentina, Australia, Austria, Belgium, Brazil, Canada, France, Germany, Italy, New Zealand, Poland, Spain, the United Kingdom and the United States) 61% of the women and 72% of the men with STEMI had an angiography performed year 1999-2006 (ref Dey et al, Heart 2009;95:20-26).

The reviewer suggests:
9.Advise to have the tables and figures at the end of the manuscript
Answer:
We followed the author instructions we had gotten, but we have now omitted the table from the manuscript file and uploaded it as a separate file.

The reviewer suggests:
10.In the final Conclusion section, I advise to focus on the persistent mortality gap among women and men presenting with STEMI
Answer:
We agree. Done.

VERSION 2 – REVIEW

REVIEWER	Hani Jneid, MD Baylor College of Medicine Houston, TX - USA I have no competing/conflicts of interest -
REVIEW RETURNED	01/02/2012

THE STUDY	need to further enhance the manuscript writing, especially the abstract

REVIEWER	Raffaele Bugiardini Professor of Cardiology Department of Internal Medicin, Section of Cardiology University of Bologna

	competing interests none
REVIEW RETURNED	08/02/2012

The reviewer filled out the checklist but made no further comment.