Author’s response to reviews

Title: Renal dysfunction in STEMI-patients undergoing primary angioplasty: higher prevalence but equal prognostic impact in female patients, an observational cohort study of the Belgian STEMI registry

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Author’s response to reviews: see over
Gent, 15 November 2012-11-15

We would like to thank the reviewers for their thorough review and constructive remarks. All remarks are addressed underneath in a point-by-point description. We revised the title and the manuscript in light of the remarks of the reviewers.

**Reviewer 1**

-A flow chart is suggested to follow the originally 9,535 patients down to 1,638 in the end participating in the study.

*A flow chart (Fig 1) was added to illustrate the flow of the originally registered patients down to the 1,638 patients treated with primary PCI in the 8 tertiary care centers.*

- It is also of interest to know what the catchment area (geographically and in numbers) is for this tertiary center with PCI-facilities. I.e. the generalisability of the study.

*Belgium constitutes a catchment area of 11.000.000 inhabitants. At the moment of the study Belgium comprised 27 PCI-centres (capable of primary PCI 24/24, 7/7); 25 of these participated in the registry. We included patients admitted to 8 of these 25 participating PCI-centres, roughly accounting for 20,3% of invasive managed STEMI patients.*

*The 8 participating centres are spread over Belgium:*  
-5 (of 12) in Flanders (± 6,400,000 inhabitants)  
-2 (of 6) in Brussels (± 1,200,000 inhabitants)  
-1 (of 7) in Wallonia (± 3,500,000 inhabitants)

- The algorithm used for eGFR, the reference is given but makes it easier for the reader if the calculation is given directly in the article.

*The CKD-EPI algorithm for calculation of eGFR was added in ‘Subjects and Methods’* → *GFR measurement.*

- Data were monitored in 10% of all patient files but there are no given results of the monitoring – please add this

*Data were monitored in 10%, results of this monitoring were added: ‘96% concordance between source documents and case report forms’.*

- Only 20% women were included, less than is the usual case. Why?

*Only 20% women were included: the original database consisted of 9,535 patients in Feb. 2011, (24.7% women), of these 8,073 were treated with primary PCI (23.8% women); which is comparable to literature. For this study we analyzed 1,638 PCI treated patients out of 1,751 (20.7% women) patients who were admitted in 8 participating tertiary care centers, of these only 20.6% were women; we do not have a clear explanation for this: it is not clear whether this finding might be due to chance, we do not think that the differences*
can be explained by regional differences since the participating centres are spread over Belgium.

- Table 1: Definition of “ischemic time”?

Table 1: Definition of ischemic time: Ischemic time is defined as the time between the onset of symptoms and primary PCI (=symptom to balloon). This was added in the table.

- The authors call this a “large cohort” when it comprises only 17% of the whole STEMI cohort registered at the same time. Rephrase please.

Discussion: ‘Large cohort’: ...(8,073 were treated with primary PCI in the registry, of them 1,638 (20.3%) were included in the analysis) this was rephrased as follows: ‘In a sub-analysis, including 20.3 % of of Belgian STEMI patients undergoing pPCI for STEMI’

- I do not agree that this data set represents a nationwide cohort as only 17% of the nationwide cohort was analysed regarding kidney function – it cannot be generalised to the whole population. Please rephrase this even if this limitation is alluded to later in limitations.

Strengths and Limitations: ‘Nationwide cohort’ was rephrased as follows: ‘This study is unique as it represents the first dataset that links gender, renal dysfunction, assessed by the CKD-EPI equation, and outcomes in a subgroup (20.3%) of PCI-treated STEMI patients included in the Belgian STEMI registry’

- Please add in title what type of study, using general terms (e.g. observational, cohort study). It is not clearly stated in the title that women have more RI at admission and nothing about what the authors found of prognostic impact, only that they studied the same.

Title: The title was adapted accordingly:

‘Renal dysfunction in STEMI-patients undergoing primary angioplasty: higher prevalence but equal prognostic impact in female patients, an observational cohort study from the Belgian STEMI registry’

-Abstract: Is it really a multicentre study as only one tertiary center was analysed?

Abstract: This is really a multicentre study as it included patients from 8 tertiary care centers (Ghent, Aalst, Antwerp, Leuven, Brussels (2), Mont Godinne and Bruges). The following sentence in ’Methods and Subjects’ and ’Results’ → Study population was misleading and was corrected as follows:

‘We retrospectively collected admission values of creatinine of patients (N= 1,751, 20.7% women) admitted in one of the eight tertiary care centers that participated in this sub-analysis.’

→

‘We retrospectively collected admission values of creatinine of patients (N= 1,751, 20.7% women) admitted in eight tertiary care centers that participated in this sub-analysis.’
Reviewer 2:

Major:
1) It is not clear whether female sex is an independent predictor of in-hospital mortality in this study. The authors should identify and report predictors of in-hospital mortality in the overall population. As they used the TIMI risk score which incorporates several variables already, they should perform a multivariable logistic regression including renal impairment, TIMI risk score and female sex in the entire population, assessing the impact of these 3 variables on mortality.

- When correcting for components of TIMI risk score in the 'total STEMI-registry population treated with primary PCI' (N=8,073) female gender was an independent predictor of mortality (OR 1.46, 95% CI 1.12-1.89). The results of this analysis are submitted for publication elsewhere.

-We suppose that the 'overall population' alluded to in the reviewers comment is the population of this sub-analysis (N=1,638) (we don't have creatinine values of the other registry patients).

➔ In a multivariable analysis, including female gender, renal dysfunction as categorical variables and TIMI risk score as a continuous variable, renal dysfunction (OR 2.71, 95% CI: 1.56-4.69) and TIMI risk score (1.47, 95% CI 1.35-1.6) were statistically significant predictors of in-hospital mortality. Female gender was associated with a trend towards higher mortality (OR 1.45, 95% CI: 0.8-2.63) in this sub-analysis.

➔The sample size of this sub-analysis was too small to show a statistical significant impact of female gender on mortality; however the obtained Odd Ratio for female gender was similar to the Odds Ratio for female gender in the analysis of the ‘total STEMI population treated with pPCI” (where female gender was an independent predictor of mortality).

2) Avoid addressing predictors of in-hospital mortality in the subgroup of women vs. those among men. This reduces the power of such regression analyses. As sex-renal impairment interaction is not significant in the overall population, sex-strata analyses assessing the impact of renal impairment on outcomes should be reported only as a descriptive finding.

The text was adapted accordingly.

3) The imbalance in baseline clinical characteristics between women and men is high, and this is in agreement with the literature. The TIMI risk score in women is higher than in men. The authors should report whether TIMI risk score is a predictor of in-hospital mortality in the overall population (point 1).

TIMI risk score is indeed an independent predictor of mortality in the overall population (N=1,638). (cfr 1) This was added in the text.

After assessment of point 1 it could be easier to speculate whether differences in mortality between women and men can be totally explained by differences between the two groups in
the measured baseline clinical characteristics, including renal dysfunction and eventually TIMI risk score, or sex-specific differences and/or possibly unmeasured factors could contribute to such mortality difference.

**Women have higher TIMI risk scores and higher incidence of renal dysfunction, both factors predict independently mortality.** However the TIMI risk score is a weighed score and female sex is inexplicitly incorporated in the TIMI risk score: the prevalences of older age, ischemic times>4h, hypotension and/or tachycardia on admission, Killip class >I, diabetes, hypertension and body weights <76 kg, in particular), are significantly higher in female STEMI patients leading to higher TIMI scores. To explain differences in mortality between men an women a larger multivariable analysis is needed, including components of TIMI risk score, renal dysfunction and other possible factors that could have impact on mortality (such as coronary anatomy, bleeding and other complications, ...). This was not the objective of our analysis.

4) Provide sensitivity analysis after exclusion of missing values, to verify whether results of the present analysis are confirmed.

*We feel a bit uncertain about this question as the multivariable analysis was based on complete records, hence the issue of missing values is not applicable in our opinion.*

Minor essential revisions

1) The following sentence “renal dysfunction could be one of the most important reasons why women with STEMI die more than men” should be reformulated considering the potential prognostic impact of TIMI risk score in the overall population (if the latter is verified) and its difference between sexes.

-We evaluated the prognostic impact of the TIMI risk score in men and women separately for all patients included in the registry that were treated with primary PCI (N= 8,073). The results of this analysis are submitted for publication elsewhere but demonstrated that the TIMI risk score had an equal prognostic performance in both men and women in predicting in-hospital mortality rates (c statistic in women: 0.84 (95% CI 0.81-0.87), c statistic in men: 0.89 (95% CI: 0.87-0.91).

-Renal dysfunction, defined by an eGFR <60ml/min/m², predicts independently of the TIMI risk score in-hospital mortality (in the overall population (N=1,638) and in men and women separately); since this condition occurs more in women than in men and taken into account that no difference in mortality between men and women with preserved renal function was observed, we speculate that renal function could be an important reason why women die more than men.

→ the sentence was adapted as follows ‘we speculate that renal dysfunction could be an important reason why women with STEMI die more than men’