PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Association between gender and short term outcome in ST elevation myocardial infarction patients participating in the international, prospective, randomised Administration of Ticagrelor in the cath Lab or in the Ambulance for New ST elevation myocardial Infarction to open the Coronary artery (ATLANTIC) trial: a prespecified analysis
AUTHORS	Venetsanos, Dimitrios; Sederholm Lawesson, Sofia; Alfredsson, Joakim; Janzon, magnus; Cequier, Angel; Chettibi, Mohamed; Goodman, Shaun; van 't Hof, Arnoud; Montalescot, Gilles; Swahn, Eva

VERSION 1 - REVIEW

REVIEWER	Erne Paul Departement of Biomedicine, Basel /Siwitzland Uinverisity Hospital, Helebstrasse 20, 4031 Basel I am prsesident of the Siss registry on mycardial infarctions (AMIS Plus)
REVIEW RETURNED	09-Dec-2016

GENERAL COMMENTS	This authors have adrressed a study question which dealt with gender diffrence and has attrcated many work, already published and which need to be cited. Th. Pilgrim, D. Heg, K. Tal, P. Erne, D. Radovanovic, S. Windecker, P. Juni: Age-and Gender-related Disparities in Primary Percutaneous Coronary Interventions for Acute Myocardial Infarction. PloS One 2015; 10 (9):e0137047. doi: 10.1371/journal.pone.0137047 Roffi M, Radovanovic D, Erne P, Urban P, Windecker S, Eberli FR; for the AMIS Plus Investigators. Gender-related mortality trends among diabetic patients with ST-segment elevation myocardial infarction: insights from a nationwide registry 1997-2010. EHJ ACC 2013; 2(4):342-9 Radovanovic D, Erne P. Gender difference in the application of reperfusion therapy in patients with acute myocardial infarction. Cardiology 2009;114:164-6. (editorial) Radovanovic D, Erne P, Urban P, Bertel O, Rickli H, Gaspoz J-M on behalf of the AMIS Plus Investigators: Gender differences in management and outcomes in patients with acute coronary syndromes. Results on 20,290 patients from the AMIS Plus Registry. Heart 2007; 93: 1369-75.

	The authors are asked to provide the following items: 1. How was qualiity of data checked in the partcipating centers? 2. Hiw were pateints recruidted coonsequetntly or not, and how can the authors not that data can be transformed to the knowlegde to other registries. 3. What is really novel? Were data alyzed by multivariate analysis are females not only older when they entered the study) 4. Are only first STEMI considered?

REVIEWER	Vojko Kanic University Medical Centre Maribor, Slovenia
REVIEW RETURNED	24-Dec-2016

GENERAL COMMENTS	General comments Overall, this paper is well written and provides important evidence regarding the gender differences in outcomes in STEMI patients treated with PPCI. However, this paper requires more details and insights, especially in terms of methods, statistics and discussion. There were different populations in the article and they were treated differently. The adjustments for treatment modalities and confounders need to be extensively revised and expanded. Specific comments: 1. Abstract- line 45 -Grammatical error: …..“longer pre-hospital delays and better TIMI flow in the infarct-related. « probably “artery”. 2. Figures 2 and 3 are almost impossible to read. Please submit figures 2 and 3 with higher resolution in the revision. 3. Page 6, line 16: What was the reason for including the “time from symptom onset to pre-PCI electrocardiogram [ECG]” (≈ time from the onset of symptoms to the catheterization laboratory) in multivariate analysis instead of total ischaemic time or door-to-balloon time, which correlate with mortality? 4. Women were more often treated with femoral access. On the other hand, GPI and intravenous anticoagulation therapy, which increase the risk of bleeding, were less often used in women. Women were also significantly more often left without revascularization. Furthermore, bivalirudin was used more often in women. All these factors could have influenced bleeding and the mortality risk in these populations. To strengthen the case for sex, the results of the full multivariate analysis should be shown. I would have expected at least access site, heparin, bivalirudin and “no revascularization” to be included in multivariate analysis to adjust for the differences in populations. 5. Thromboaspiration was more frequently performed in men. This indirectly means that greater thrombotic burden was present in men. The higher acute-ST rate (which might potentially be expected in the group with more bivalirudin usage, i.e., women) could have been influenced by higher thrombotic burden in men. Please comment. 6. Table 1- More women were without revascularization. 15.2 % of patients without revascularization in the STEMI population is high. Primary PCI is the treatment of choice for patients presenting with acute STEMI if catheterization facilities and experienced interventional cardiologists are immediately available. According to the aim of the study (“To evaluate gender differences in outcomes in STEMI patients treated with PPCI«), these patients should be removed from the study, or this covariate should be included in the multivariate analysis. 7. “Post-PCI TIMI flow” might be influenced by adjunctive GPI usage

	and PCI (which were more often used in men). Indeed, TIMI flow before PCI was significantly better in women, but TIMI flow after PCI (which did occur more often in men and more GPI were used) was similar in both groups. Please comment. It would be interesting to see the TIMI flow, mortality and bleeding in the two populations without the “no-revascularization” group). 8. There is a question as to whether the results of this perfectly performed randomised study really correspond to “real-life” data? In every-day practice, it is almost impossible to achieve such a short delay in treatment as that achieved in the ATLANTIC study. Data from registries indicate that the time delays in STEMI are usually much longer. Furthermore, the exclusion criteria for the ATLANTIC study (non-steroidal anti-inflammatory drugs, oral anticoagulants, cardiogenic shock or severe haemodynamic instability in STEMI patients), do not always fit the real-life situation seen in STEMI patients. This should also be mentioned in the discussion.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1: Erne Paul

Q1: This authors have adrressed a study question which dealt with gender diffrence and has many work, already published and which need to be cited.

Th. Pilgrim, D. Heg, K. Tal, P. Erne, D. Radovanovic, S. Windecker, P. Juni: Age-and Gender-related Disparities in Primary Percutaneous Coronary Interventions for Acute Myocardial Infarction. PloS One 2015; 10 (9):e0137047. doi: 10.1371/journal.pone.0137047

Roffi M, Radovanovic D, Erne P, Urban P, Windecker S, Eberli FR; for the AMIS Plus Investigators. Gender-related mortality trends among diabetic patients with ST-segment elevation myocardial infarction: insights from a nationwide registry 1997-2010. EHJ ACC 2013; 2(4):342-9

Radovanovic D, Erne P. Gender difference in the application of reperfusion therapy in patients with acute myocardial infarction. Cardiology 2009;114:164-6. (editorial)

Radovanovic D, Erne P, Urban P, Bertel O, Rickli H, Gaspoz J-M on behalf of the AMIS Plus Investigators: Gender differences in management and outcomes in patients with acute coronary syndromes. Results on 20,290 patients from the AMIS Plus Registry.
Heart 2007; 93: 1369-75.

A1: We agree that the gender perspective during the last decades has been addressed in quite many studies, not the least from our own group. One important point that we make in the manuscript is that many of the former studies are quite old and therefore do not reflect todays clinical practice as well as the current analysis. Anyhow we do think that to have pre-planned sub-studies on the gender perspective in important RTCs add value to the information given by observational registry-studies. Pre-specified analyses based on gender are also advocated by regulatory authorities like the Food and Drug Administration. Of course it is a difficult issue to do the comparison as the balance in included women and men, especially in STEMI populations, is quite skew. To get a proper balance it would be necessary to do power calculations on each gender and continue inclusion until enough women are included. Anyhow, in comparison with observational registry studies the groups randomised in RCTs have minimised the inequality as much as possible. On of the suggested references by Pilgrim et al is now added.

Q2: How was qualiity of data checked in the partcipating centers?

A2: ATLANTIC is a randomised double blind clinical trial, with central randomisation, 100% local monitoring of the medical records in the centers, CRF cross-checking, declaration of all adverse events, mandatory pharmacovigilance declarations when AE were related to the drug, adjudication of all the events declared by the investigators by an independent clinical endpoint committee. As we have stated and cited in the manuscript, full details of the study design and primary results have previously been published.

Q3: Hiw were pateints recruidted coonsequetntly or not, and how can the authors not that data can be transformed to the knowlegde to other registries.
A3: ATLANTIC is not a registry but a randomised clinical trial, and all randomised patients were consecutive patients with a randomisation number allocated when they fulfilled the inclusion/exclusion criteria and when the investigator agreed to enrol the patients. Patients with exclusion criteria were of course not randomised and are not part of the study.
Q4: What is really novel? Were data analyzed by multivariate analysis are females not only older when they entered the study)
A5: Only a few randomised trials of STEMI patients treated with primary PCI (PPCI) have reported results in the context of gender (ref 11 and 12) and they are by now quite old. New treatment modalities have since then come up. The novelty in this study is that all patients in this randomised trial of exclusively STEMI-patients were treated according to current guidelines with modern management and treatment that could contribute to improved ischemic and bleeding outcomes in especially female STEMI patients.
Different multivariable models were used for adjustment, including age as the most important variable to adjust for when comparing men and women with STEMI. The results of the multivariate analyses are presented before and after adjustment. (See statistics for information on details of the multivariate analyses, including variables in the models)

Q5: Are only first STEMI considered?
A5: No. Prior MI was not an exclusion criterion.
Reviewer 2: Vojko Kanic
The adjustments for treatment modalities and confounders need to be extensively revised and expanded.
Q1: Abstract- line 45 -Grammatical error: ….."longer pre-hospital delays and better TIMI flow in the infarct-related. « probably "artery".
A1: Corrected.
Q2: Figures 2 and 3 are almost impossible to read. Please submit figures 2 and 3 with higher resolution in the revision.
A2: We are sorry. This will be dealt with in the revised version.
Q3: Page 6, line 16: What was the reason for including the "time from symptom onset to pre-PCI electrocardiogram [ECG]" (≈ time from the onset of symptoms to the catheterization laboratory) in multivariate analysis instead of total ischaemic time or door-to-balloon time, which correlate with mortality?
A3: As the pre-PCI ECG was taken very near to the start of PCI this is as near total ischemic time we could come, including both patient and system delay. We agree anyhow that "real" total ischemic time i.e. from symptom onset to reperfusion would have been the perfect variable to use.

Q4: Women were more often treated with femoral access. On the other hand, GPI and intravenous anticoagulation therapy, which increase the risk of bleeding, were less often used in women. Women were also significantly more often left without revascularization. Furthermore, bivalirudin was used more often in women. All these factors could have influenced bleeding and the mortality risk in these populations. To strengthen the case for sex, the results of the full multivariate analysis should be shown. I would have expected at least access site, heparin, bivalirudin and "no revascularization" to be included in multivariate analysis to adjust for the differences in populations.
A4: We very much appreciate your concern about this issue. Anyhow, as the events were very few we had to choose those factors we deemed most important for the outcome. Adding the extra variables mentioned such as the access site, would most probably only marginally have changed the point estimate for bleeding events towards a less significant adjusted difference between genders. However, adjustment for the 14 variables we used in the multivariable analysis already changed the point estimate toward the same direction, from clear significant unadjusted differences to non-significant adjusted difference. Therefore adding the variables mentioned would most probably not

change our results. As bleeding in bivalirudin vs UFH only occurred when GPI was administered together with UFH we chose not to use these variables in the multivariable model. We do not entirely agree that “no revascularisation” should be included as the reason for not performing a PCI or CABG may vary. As normal coronary arteries did not differ between genders that is not the explanation, and we cannot exclude that patients not revascularised were sicker or had other reasons for not being treated invasively.
Q5: Thromboaspiration was more frequently performed in men. This indirectly means that greater thrombotic burden was present in men. The higher acute-ST rate (which might potentially be expected in the group with more bivalirudin usage, i.e., women) could have been influenced by higher thrombotic burden in men. Please comment.
A5: Thank you for this comment. We are anyhow not convinced that the higher acute-ST rate mirrors the thrombotic burden in the acute stage of STEMI patients and the ATLANTIC study was not powered for an outcome of acute-ST rate.
Q6: Table 1- More women were without revascularization. 15.2 % of patients without revascularization in the STEMI population is high. Primary PCI is the treatment of choice for patients presenting with acute STEMI if catheterization facilities and experienced interventional cardiologists are immediately available. According to the aim of the study (“To evaluate gender differences in outcomes in STEMI patients treated with PPCI«), these patients should be removed from the study, or this covariate should be included in the multivariate analysis.
A6: Please see A4.
Q7: “Post-PCI TIMI flow” might be influenced by adjunctive GPI usage and PCI (which were more often used in men). Indeed, TIMI flow before PCI was significantly better in women, but TIMI flow after PCI (which did occur more often in men and more GPI were used) was similar in both groups. Please comment. It would be interesting to see the TIMI flow, mortality and bleeding in the two populations without the “no-revascularization” group).
A7: Interesting and “tricky” comment, but we did not do this analysis. Anyhow, as the success rate was the same in both genders and the TIMI flow cannot be better after a procedure if it was good even before this should most probably not have influenced the outcome and it would rather have been to the favor of women and thus could not explain the higher mortality in them.

Q8: There is a question as to whether the results of this perfectly performed randomised study really correspond to “real-life” data? In every-day practice, it is almost impossible to achieve such a short delay in treatment as that achieved in the ATLANTIC study. Data from registries indicate that the time delays in STEMI are usually much longer. Furthermore, the exclusion criteria for the ATLANTIC study (non-steroidal anti-inflammatory drugs, oral anticoagulants, cardiogenic shock or severe haemodynamic instability in STEMI patients), do not always fit the real-life situation seen in STEMI patients. This should also be mentioned in the discussion.
A8: This is now added among limitations.

VERSION 2 – REVIEW

REVIEWER	Paul Erne Departemnt of biomedicine , Unibesity Hospital, Basel None, I was pressident of AMIs Plus 1997.2016, the Swiss Rgristry in MI
REVIEW RETURNED	30-Jan-2017

GENERAL COMMENTS	Comments to review regarding manuscript: Women with STEMI, a high risk group for short-term mortality. Insights from the ATLANTIC study. Editorial Requirements:

	- Please revise your title to state the research question, study design, and setting. This is the preferred format for the journal. - Done - Please revise the 'Article summary' section to consist of the heading: 'Strengths and limitations of this study', contain up to five short bullet points, no longer than one sentence each, that relate specifically to the methods of the study reported. – This has now been added. We thank the reviewers for the comprehensive review of our paper. Below are our answers to all given comments from each reviewer. Reviewer 1: Erne Paul Q1: This authors have adrressed a study question which dealt with gender diffrence and has many work, already published and which need to be cited. Th. Pilgrim, D. Heg, K. Tal, P. Erne, D. Radovanovic, S. Windecker, P. Juni: Age-and Gender-related Disparities in Primary Percutaneous Coronary Interventions for Acute Myocardial Infarction. PloS One 2015; 10 (9):e0137047. doi: 10.1371/journal.pone.0137047 Roffi M, Radovanovic D, Erne P, Urban P, Windecker S, Eberli FR; for the AMIS Plus Investigators. Gender-related mortality trends among diabetic patients with ST-segment elevation myocardial infarction: insights from a nationwide registry 1997-2010. EHJ ACC 2013; 2(4):342-9 Radovanovic D, Erne P. Gender difference in the application of reperfusion therapy in patients with acute myocardial infarction. Cardiology 2009;114:164-6. (editorial) Radovanovic D, Erne P, Urban P, Bertel O, Rickli H, Gaspoz J-M on behalf of the AMIS Plus Investigators: Gender differences in management and outcomes in patients with acute coronary syndromes. Results on 20,290 patients from the AMIS Plus Registry. Heart 2007; 93: 1369-75. A1: We agree that the gender perspective during the last decades has been addressed in quite many studies, not the least from our own group. One important point that we make in the manuscript is that many of the former studies are quite old and therefore do not reflect todays clinical practice as well as the current analysis. Anyhow we do think that to have pre-planned sub-studies on the gender perspective in important RTCs add value to the information given by observational registry-studies. Pre-specified analyses based on gender are also advocated by regulatory authorities like the Food and Drug Administration. Of course it is a difficult issue to do the comparison as the balance in included women and men, especially in STEMI populations, is quite skew. To get a proper balance it would be necessary to do power calculations on each gender and continue inclusion until enough women are included. Anyhow, in comparison with observational registry studies the groups randomised in RCTs have minimised the inequality as much as possible. On of the suggested references by Pilgrim et al is now added. Q2: How was qualiity of data checked in the partcipating centers? A2: ATLANTIC is a randomised double blind clinical trial, with central randomisation, 100% local monitoring of the medical records in the centers, CRF cross-checking, declaration of all adverse events,

	mandatory pharmacovigilance declarations when AE were related to the drug, adjudication of all the events declared by the investigators by an independent clinical endpoint committee. As we have stated and cited in the manuscript, full details of the study design and primary results have previously been published. Q3: Hiw were pateints recruidted coonsequetntly or not, and how can the authors not that data can be transformed to the knowlegde to other registries. A3: ATLANTIC is not a registry but a randomised clinical trial, and all randomised patients were consecutive patients with a randomisation number allocated when they fulfilled the inclusion/exclusion criteria and when the investigator agreed to enrol the patients. Patients with exclusion criteria were of course not randomised and are not part of the study. Q4: What is really novel? Were data analyzed by multivariate analysis are females not only older when they entered the study) A5: Only a few randomised trials of STEMI patients treated with primary PCI (PPCI) have reported results in the context of gender (ref 11 and 12) and they are by now quite old. New treatment modalities have since then come up. The novelty in this study is that all patients in this randomised trial of exclusively STEMI-patients were treated according to current guidelines with modern management and treatment that could contribute to improved ischemic and bleeding outcomes in especially female STEMI patients. Different multivariable models were used for adjustment, including age as the most important variable to adjust for when comparing men and women with STEMI. The results of the multivariate analyses are presented before and after adjustment. (See statistics for information on details of the multivariate analyses, including variables in the models) Q5: Are only first STEMI considered? A5: No. Prior MI was not an exclusion criterion. Reviewer 2: Vojko Kanic The adjustments for treatment modalities and confounders need to be extensively revised and expanded. Q1: Abstract- line 45 -Grammatical error: …..“longer pre-hospital delays and better TIMI flow in the infarct-related. « probably “artery”. A1: Corrected. Q2: Figures 2 and 3 are almost impossible to read. Please submit figures 2 and 3 with higher resolution in the revision. A2: We are sorry. This will be dealt with in the revised version. Q3: Page 6, line 16: What was the reason for including the “time from symptom onset to pre-PCI electrocardiogram [ECG]” (≈ time from the onset of symptoms to the catheterization laboratory) in multivariate analysis instead of total ischaemic time or door-to-balloon time, which correlate with mortality? A3: As the pre-PCI ECG was taken very near to the start of PCI this is as near total ischemic time we could come, including both patient and system delay. We agree anyhow that “real” total ischemic time i.e. from symptom onset to reperfusion would have been the perfect variable to use.

	Q4: Women were more often treated with femoral access. On the other hand, GPI and intravenous anticoagulation therapy, which increase the risk of bleeding, were less often used in women. Women were also significantly more often left without revascularization. Furthermore, bivalirudin was used more often in women. All these factors could have influenced bleeding and the mortality risk in these populations. To strengthen the case for sex, the results of the full multivariate analysis should be shown. I would have expected at least access site, heparin, bivalirudin and “no revascularization” to be included in multivariate analysis to adjust for the differences in populations. A4: We very much appreciate your concern about this issue. Anyhow, as the events were very few we had to choose those factors we deemed most important for the outcome. Adding the extra variables mentioned such as the access site, would most probably only marginally have changed the point estimate for bleeding events towards a less significant adjusted difference between genders. However, adjustment for the 14 variables we used in the multivariable analysis already changed the point estimate toward the same direction, from clear significant unadjusted differences to non-significant adjusted difference. Therefore adding the variables mentioned would most probably not change our results. As bleeding in bivalirudin vs UFH only occurred when GPI was administered together with UFH we chose not to use these variables in the multivariable model. We do not entirely agree that “no revascularisation” should be included as the reason for not performing a PCI or CABG may vary. As normal coronary arteries did not differ between genders that is not the explanation, and we cannot exclude that patients not revascularised were sicker or had other reasons for not being treated invasively. Q5: Thromboaspiration was more frequently performed in men. This indirectly means that greater thrombotic burden was present in men. The higher acute-ST rate (which might potentially be expected in the group with more bivalirudin usage, i.e., women) could have been influenced by higher thrombotic burden in men. Please comment. A5: Thank you for this comment. We are anyhow not convinced that the higher acute-ST rate mirrors the thrombotic burden in the acute stage of STEMI patients and the ATLANTIC study was not powered for an outcome of acute-ST rate. Q6: Table 1- More women were without revascularization. 15.2 % of patients without revascularization in the STEMI population is high. Primary PCI is the treatment of choice for patients presenting with acute STEMI if catheterization facilities and experienced interventional cardiologists are immediately available. According to the aim of the study (“To evaluate gender differences in outcomes in STEMI patients treated with PPCI«), these patients should be removed from the study, or this covariate should be included in the multivariate analysis. A6: Please see A4. Q7: “Post-PCI TIMI flow” might be influenced by adjunctive GPI usage and PCI (which were more often used in men). Indeed, TIMI flow before PCI was significantly better in women, but TIMI flow after PCI (which did occur more often in men and more GPI were used) was similar in both groups. Please comment. It would be interesting to see the TIMI flow, mortality and bleeding in the two populations without the “no-revascularization” group). A7: Interesting and “tricky” comment, but we did not do this analysis. Anyhow, as the success rate was the same in both genders and the TIMI flow cannot be better after a procedure if it was good even before this should most probably not have influenced the outcome

	and it would rather have been to the favor of women and thus could not explain the higher mortality in them. Q8: There is a question as to whether the results of this perfectly performed randomised study really correspond to “real-life” data? In every-day practice, it is almost impossible to achieve such a short delay in treatment as that achieved in the ATLANTIC study. Data from registries indicate that the time delays in STEMI are usually much longer. Furthermore, the exclusion criteria for the ATLANTIC study (non-steroidal anti-inflammatory drugs, oral anticoagulants, cardiogenic shock or severe haemodynamic instability in STEMI patients), do not always fit the real-life situation seen in STEMI patients. This should also be mentioned in the discussion. A8: This is now added among limitations. The reviewer also provided a file in addition to these comments. Please contact the publisher for full details.

REVIEWER	Vojko Kanic University Medical Centre Maribor, Slovenia
REVIEW RETURNED	06-Feb-2017

GENERAL COMMENTS	General comments The authors have made minimal changes to the article (Different title and one sentence in the Limitation). They did successfully comment all my remarks except the most important one – the remark regarding multivariate analysis to adjust for the differences in populations. I suggest that a statistician with medical knowledge checks the adjustment variables included in the multivariate analysis (see my previous comments). If he finds the adjustments sufficient, the article could be accepted.

REVIEWER	Jesung You Yonsei University College of Medicine Department of Emergency Medicine
REVIEW RETURNED	08-Mar-2017

GENERAL COMMENTS	Thank you for opportunity of reviewing this article. The article is well written based on statistically clear results. I think that author should clarify some pint. 1. I think that results of baseline characteristics were similiar to results of Univariable Cox analysis. However, please, attach results of Univariable Cox analysis in appendix - for clarifying selection of variable for adjusting in multivariable Cox analysis. Additionally please, clarify selection for variable of adjusting in multi Cox ($p<0.05$?, $p<0.1$? in Univariable Cox) 2. I think that times for min from hospital to PCI and min pre-PCI to Post PCI may also be significant in Uni Cox. Why did you include this as variabes in Multi- Cox analysis? although you do not need to reanalyze this, please, clearly explain this point based on clinical implication

VERSION 2 – AUTHOR RESPONSE

Reviewer 1: Erne Paul
The first reviewer had no additional comments/requirements.
Reviewer 2: Vojko Kanic
Q1: General comments
The authors have made minimal changes to the article (Different title and one sentence in the Limitation).
They did successfully comment all my remarks except the most important one – the remark regarding multivariate analysis to adjust for the differences in populations.
I suggest that a statistician with medical knowledge checks the adjustment variables included in the multivariate analysis (see my previous comments). If he finds the adjustments sufficient, the article could be accepted.
A1: We have now revised our multivariable analyses (for all outcomes) by including revascularisation or not, access site and type of anticoagulation (bivalirudin / UFH) as covariates in our model. There was only one impact on conclusions – the p-value associated with all-cause mortality (women vs men independent of randomised treatment) moved from 0.06 to 0.04 that is considered formally significant, although the actual impact on the HR was obviously minor. Nothing else was materially affected. Accordingly, we have revised abstract, methods and discussion as well as we have included the new results in figures, tables and supplementary material.
Reviewer 3: Jesung You
Q1: I think that results of baseline characteristics were similiar to results of Univariable Cox analysis. However, please, attach results of Univariable Cox analysis in appendix - for clarifying selection of variable for adjusting in multivariable Cox analysis. Additionally please, clarify selection for variable of adjusting in multi Cox ($p<0.05$?, $p<0.1$? in Univariable Cox)
A1: Selection of covariates included in the multivariable analysis was based on previous studies and clinical experience. Univariate analysis was not performed. However, this is a common practice in observational studies and we included 19 covariates in our multivariable analysis that, we believe, incorporated all possible predictors of adverse outcomes in a STEMI population.
Q2: I think that times for min from hospital to PCI and min pre-PCI to Post PCI may also be significant in Uni Cox. Why did you include this as variabes in Multi- Cox analysis? although you do not need to reanalyze this, please, clearly explain this point based on clinical implication
A2: The timing variables were all highly correlated, so time from symptom onset to pre-hospital ECG was selected as the single best surrogate for a general marker of time-to-treatment; this was also the time-variable with the greatest difference between genders. Inclusion of multiple correlated variables risked diluting the effect of them and causing problems for model fitting.

VERSION 3 – REVIEW

REVIEWER	Vojko Kanic University Medical Center Maribor Slovenia
REVIEW RETURNED	13-May-2017

GENERAL COMMENTS	I would like to congratulate to the authors. The present article is a valuable contribution to the unresolved issue of the gender impact on the outcome in STEMI patients treated with modern therapy.

REVIEWER	JESUNG YOU YONSEI UNIVERSITY COLLEGE OF MEDICINE
REVIEW RETURNED	15-May-2017

GENERAL COMMENTS	Thank you for your comments. I agree with your comments. For readers, please add your comments to method of manuscript after summarizing your comment below. In addition, please clarify reference for your previous study. A1: Selection of covariates included in the multivariable analysis was based on previous studies and clinical experience. Univariate analysis was not performed. However, this is a common practice in observational studies and we included 19 covariates in our multivariable analysis that, we believe, incorporated all possible predictors of adverse outcomes in a STEMI population.

VERSION 3 – AUTHOR RESPONSE

Comments to review regarding manuscript:
Association between gender and short term outcome in ST elevation myocardial infarction patients treated with novel antiplatelet therapy, participating in the international, prospective, randomised Administration of Ticagrelor in the cath Lab or in the Ambulance for New ST elevation myocardial Infarction to open the Coronary artery (ATLANTIC) trial
Editorial Requirements:
-Please revise your title to state the research question, study design, and setting (location), ensuring that you do not include acronyms or abbreviations. This is the preferred format for the journal.

We have accordingly revised the title of the manuscript and we hope that this version satisfies the preferred format of the journal
We thank the reviewers for their additional comments/requirements. Below are our answers to all given comments from each reviewer.
Reviewer 2: Vojko Kanic
I would like to congratulate to the authors. The present article is a valuable contribution to the unresolved issue of the gender impact on the outcome in STEMI patients treated with modern therapy.

Thank you!
Reviewer 3: Jesung You
Thank you for your comments. I agree with your comments.
For readers, please add your comments to method of manuscript after summarizing your comment below. In addition, please clarify reference for your previous study.

A1: Selection of covariates included in the multivariable analysis was based on previous studies and clinical experience. Univariate analysis was not performed. However, this is a common practice in observational studies and we included 19 covariates in our multivariable analysis that, we believe, incorporated all possible predictors of adverse outcomes in a STEMI population.

Done.