International Journal of Cardiology

Sex differences in distribution, management and outcomes of combined ischemic-bleeding risk following acute coronary syndrome

--Manuscript Draft--

Manuscript Number:	IJCJOURNAL-D-20-01466R1
Article Type:	Original article
Section/Category:	1. Coronary circulation/Ischemic heart disease
Keywords:	GRACE; CRUSADE; risk scores; outcomes; management; sex
Corresponding Author:	Mohamed MOHAMED Keele Cardiovascular Research Group, Centre for Prognosis Research, Institutes of Applied Clinical Science and Primary Care and Health Sciences, Keele University Keele, United Kingdom United Kingdom
First Author:	Mohamed MOHAMED
Order of Authors:	Mohamed MOHAMED Muhammad Rashid, PhD Adam Timmis Sarah Clarke Claire Lawson Erin D. Michos, MD, MHS Chun Shing Kwok, MRCP Mark De Belder Marco Valgimigli, MD, PhD Mamas A. Mamas, DPhil
Manuscript Region of Origin:	Europe
Abstract:	<p>Background</p> <p>Risk factors for further bleeding and ischemic events after acute coronary syndrome (ACS) often overlap. Little is known about sex-based differences in the management and outcomes of ACS patients according to their combined bleeding-ischemic risk.</p> <p>Methods</p> <p>All ACS hospitalizations in the United Kingdom (2010-2017) were retrospectively analyzed, stratified by sex and bleeding-ischemic risk combination (using CRUSADE and GRACE scores). Multivariable logistic regression was performed to examine association between risk-groups and 1) receipt of guideline-recommended management and 2) in-hospital outcomes.</p> <p>Results</p> <p>Of 584,360 patients, a third of males (32.3%) and females (32.6%) were in the dual high-risk group (High CRUSADE- High GRACE). In comparison to the dual low-risk group (Low CRUSADE-Low GRACE), the dual high-risk patients of both sexes were 59-83% less likely to receive coronary angiography (CA) or percutaneous coronary intervention (PCI), 31-34% less likely to receive dual antiplatelet therapy (DAPT) on discharge, with a significant increase in odds of MACE (8-fold), all-cause and cardiac mortality (30 to 40-fold), and bleeding (40-43%). The greatest difference in management and clinical outcomes between sexes was found in the dual-high risk group where females were less likely to receive guideline-recommended therapy (PCI and DAPT), compared to males, and were more likely to experience MACE, all-cause and cardiac mortality.</p>

	<p>Conclusion</p> <p>ACS patients with dual high-risk for bleeding and recurrent ischemia, especially females, are less likely to receive guideline-recommended therapy and experience significantly worse outcomes. Novel strategies are needed to effectively manage this highly prevalent, complex patient group and address the under-treatment of females.</p>
Suggested Reviewers:	
Response to Reviewers:

Dear Professor Paolo G. Camici, Editor in Chief,

We thank the Editorial Committee and the Reviewer for their valuable comments on the manuscript entitled 'Sex differences in distribution, management and outcomes of combined ischemic-bleeding risk following acute coronary syndrome Brief title: ACS sex differences in ischemic-bleeding risk' We feel that these comments have improved the quality of our manuscript. We have attempted to answer all the comments fully as outlined in the rebuttal and tracked all new changes in the manuscript.

We hope that we have addressed all reviewers' comments sufficiently and hope that these changes will enable publication of our paper in the International Journal of Cardiology.

Yours sincerely

Mohamed Mohamed and Mamas Mamas

On behalf of submitting authors

We list our reply to the reviewer's comments in the file entitled 'Response to Reviewers' as per journal instructions.

Response to Editorial and Reviewers' comments

Editor's comments:

The authors should be commended for their efforts in conducting this investigation.

The study is of interest with a relevant sample size.

In order to harmonize the study, I would strongly suggest to divide the population in three groups: LOW-LOW (about 100000 patients), HIGH-HIGH (About 200000) and all remaining patients (intermediate group with about 300000 patients). This could facilitate statistics and improve the readability of the manuscript, making easier the evaluation of gender difference in outcome across the three groups and the comparison between the three groups in terms of baseline characteristics and outcome.

Response: We thank the editor for their comment and fully agree that this would further simplify matters. We have, therefore, decided to reclassify our cohort as per this suggestion and have updated the results accordingly.

Reviewer #1:

The study presented in this manuscript aimed to identify the gender differences in the managements and outcomes of hospitalized ACS patients with different combined bleeding-ischemic risk. Clinical data of 584 360 hospitalized patients with ACS in the United Kingdom from 2010-2017 were retrospectively analyzed. The ACS patients were divided into 9 combined bleeding-ischemic risk groups according different combinations of low, medium and high risk by the CRUSADE and GRACE scores. Based on the descriptions of this manuscript, the study found about one third of the ACS patients were classified as dual high-risk group in both men and women. In comparison to the dual low-risk group, the dual high-risk patients of both sexes were less likely to receive coronary angiography (CA), PCI, and DAPT and had much higher risks for MACE, all-cause death, cardiac death and bleeding during hospitalization. Compared with male patients with the same risk, female patients with the dual-high risk received less PCI and DAPT treatments, were more likely to experience MACE, all-cause and cardiac mortality. The study therefore concluded that female are less likely to receive guideline-recommended therapy and experience significantly worse outcomes. The main research questions are clinically relevant and important, and the results may reflect the problems or challenges in the management of ACS inpatients for men and women. But several issues need to further clarify.

My comments are in below.

1. If the study aimed to compare and assess the gender differences in performance for guidelines recommended managements of ACS with different bleeding-ischemic risk, it is better to recruited only ACS patients under 75 years old or add stratified analyses by age because the most evidence for PCI, DAPT came from RCTs included none or very small proportion patients over 75 years old and the main guidelines recommendations for the management of ACS inpatients may not suitable for patients with very old age. I think the substantial differences in utilities of CA, PCI and DAPT treatments and the MACE, in-hospital mortalities and bleeding between dual high-risk group and dual low-risk

group, and between men and women identified by this study can be largely explained by the significant differences in age among the risk groups and between men and women. While the mean ages in dual high-risk group were 77 ± 10 in men and 82 ± 10 in women, the mean ages in dual low-risk group were 54 ± 10 in men and 57 ± 10 in women. The Group 3 and group 6 had higher mean ages than group 1,2,4,5,7 and 8. And women in group 3 and group 6 and group 9 had much high mean age than men in the same groups.

Response: We thank the reviewer for their comment. Indeed, elderly patients are either excluded or underrepresented in many trials, as is the case for women, but this is the reason why we are left with very limited outcomes data in this population and also a strength of our study. We believe that our findings reflect real-world practice, in which a significant proportion of patients are elderly. Age is only a single component of GRACE, and not even included in the CRUSADE score. Therefore, many patients will still be at a dual high-risk even if aged less than 75 years and age cannot solely explain our findings. Moreover, risk groups were compared to one another within the same sex, not across sexes (e.g. Low-Low vs. High-High within males, and separately for females) so the age difference between men and women has no influence on the findings reported. In order to further simplify our argument, we have performed a sensitivity analysis that only included patients aged less than 75 years (results below and included in the Supplementary Material). As the reviewer will note, the differences in crude rates of clinical outcomes as well as receipt of invasive management and DAPT between risk groups, and between sexes in the dual high-risk group, are very similar to those found in the original cohort.

Supplementary Table 2. In-hospital management strategy and outcomes (unadjusted) in patients aged <75 years

	Low GRACE- Low CRUSADE (n=96356)		All other risk combinations (n=217,223)		High GRACE-High CRUSADE (n=63,885)	
	M (73.0%)	F (27.0%)	M (73.6%)	F (26.4%)	M (79.9%)	F (20.1%)
CA, %	76.6	77.2	69.8	67.4	57.3	51.3
PCI, %	56.7	48.9	50.1	43.9	37.5	29.4
Primary PCI, %	28.9	19.4	36.5	31.1	35.8	22.9
CABG, %	3.0	2.0	3.5	2.4	3.8	2.8
PCI planned after discharge, %	2.1	1.9	2.1	1.8	1.6	1.5
CABG planned after discharge, %	2.5	1.6	2.9	1.9	3.0	2.0
MACE*	0.9	0.9	1.8	2.7	9.7	11.7
All-cause mortality, %	0.2	0.3	1.2	2.3	9.8	12.9
Cardiac mortality, %	0.2	0.3	1.0	1.9	8.6	10.9
Reinfarction, %	0.8	0.7	0.8	0.9	1.5	1.3
All-cause bleeding, %	1.0	1.2	1.3	1.8	2.7	3.5
TIMI major bleeding, %	0.2	0.2	0.3	0.3	0.6	0.5
Discharge Medications*						
ACEI, %	90.5	85.4	88.9	84.0	76.9	68.5
Beta-blockers, %	89.2	84.6	88.1	83.3	79.6	72.2
Statins, %	96.7	94.2	95.8	93.1	88.3	84.0
Antiplatelets, %						
None	1.3	2.1	1.6	2.2	3.2	4.7
Aspirin only	6.1	8.0	7.0	8.4	13.6	15.9
P2Y12 inhibitor only	1.9	2.7	2.4	3.5	4.1	5.7
DAPT	90.7	87.2	89.0	85.9	79.1	73.8

ACEI: angiotensin converting enzyme inhibitor; CA: coronary angiography; CABG: coronary artery bypass grafting; DAPT: dual antiplatelet therapy (aspirin and any P2Y12 inhibitor); PCI: percutaneous coronary intervention; TIMI: thrombosis in myocardial infarction; MACE: major acute cardiac events (composite of cardiac mortality and reinfarction)

2. It is necessary for authors to provide information regarding missing rates of the key variables, especially those to calculate GRACE and CRUSADE score and those as outcomes, such as statuses of CA, PCI and DAPT uses. Even the multiple imputation has demonstrated less bias, it is not suitable for variables with high missing rates.

Response: Thank you, these have now been provided in Supplementary Table 1. The values were not missing at significant rate, but also not low enough to have justified exclusion as opposed to imputation.

3. Both primary PCI and early DAPT uses may lower the risks of MACE and in-hospital mortalities in these ACS patients. It is reasonable to add the two variables as potential confounders in the models to estimate the risk of the MACE and in-hospital mortality by different bleeding-ischemic risk groups in both men and women.

Response: Primary PCI would be collinear with PCI and, therefore, we cannot adjust for both. Furthermore, not all ACS cases would have required primary PCI, which is why we chose to include overall PCI instead. We have already adjusted for inpatient use of DAPT in our original submission (mentioned in the methods and quoted below) and have done so again in our reanalysis of the revised groups (Low-Low, High-High and all other risk groups) based on the editor's suggestion.

“Multiple logistic regression was used to examine the association between the combined CRUSADE-GRACE risk groups and clinical outcomes adjusting for the following variables: ethnicity, use of inpatient pharmacotherapy (inpatient DAPT, beta blockers and furosemide)”

4. Some information in Table 1 B is quite confused. It is not clear if the proportions of PCI (line 2) included also primary PCIs. If it is yes, why some proportions of PPCI were larger than the proportions of PCI (Group 3). And the proportions of CA should be larger than the proportions of PCI (or PCI+PPCI if the proportion of PCI did not include PPCI because all PCIs must be based on CA.

Response: We thank the reviewer for their comment. PCI also includes primary PCI. We understand that there was a slightly discrepancy in Group 3 as the reviewer has rightly noted and this was corrected. However, owing to the reclassification of study groups in to 3 instead of 9, as suggested by the editor, we have combined all the risk groups other than High-High and Low-Low in to one group for ease of presentation and interpretation by the wider readership.

5. There were some inconsistencies between data provided by Table 1 B and those by Figure 2A. From the Figure 2A, I found female patients with ACS in dual bleeding-ischemic risk group had higher use rates for CA, PCI and discharge DAPT than male patients in the same group in all time points. But in Table 1B, female patients with ACS in dual bleeding-ischemic risk group had lower mean use rates of CA, PCI and DAPT at discharge than male patients.

Response: We thank the reviewer for their comment. The data in Table 1B is correct and we have double checked this. However, there was a discrepancy in the axis scales/labelling in the figures and this has been corrected in Figure 2A.

6. I didn't find Table 2 and all supplementary Tables and figures in the manuscript.

Response: We thank the reviewer for their comment. All tables and supplementary material have been submitted with the initial submission but we apologise if any technical issues have not allowed you to see them. Furthermore, these files are usually checked by the editorial office before they reach reviewers, as is our experience when we review for IJC. We hope that all the material if available for you to kindly review this time round.

Reviewer #2

The manuscript for review provided the data on sex-based differences in the management and outcomes of ACS patients according to combined ischemic-bleeding risk.

The Authors performed a retrospective analysis of over 580 000 patients comprising all ACS hospitalizations in the UK between 2010 and 2017 (MINAP Project). They analyzed the distribution of ischemic (GRACE Risk Score) and bleeding risk (CRUSADE Bleeding Risk Score) between sexes and compared the adherence to the ESC guidelines and clinical outcomes. They revealed the variations in clinical characteristics, management strategies and outcomes with regard to ischemic-bleeding risk combinations. The Authors demonstrated that high GRACE risk groups were more prevalent in males than females and were less frequently treated invasively and with DAPT, especially females. This

group had worse clinical outcomes, particularly females. Dual high (CRUSADE and GRACE) group was associated with worse adherence to the guideline-recommended therapy and had significantly higher MACE and mortality. It was particularly evident in females.

The study concerns an important and clinically relevant topic. It is based on a very large nationwide ACS patient population. The results of a comprehensive analysis are clearly presented and discussed. Complex statistical tools have been applied. The study has a value of novelty. The manuscript is very well and interestingly written.

I have only one remark. The CRUSADE Bleeding Risk Score is dedicated to the NSTEMI-ACS population. Its application in STEMI patients would require some explanations and might be added to the limitations of this study.

Response: We thank the reviewer for their thorough appraisal of our manuscript for their valuable comments. We fully agree that the CRUSADE score was validated for NSTEMI-ACS population, although several studies have demonstrated its validity in the STEMI population as well (example reference below). Our rationale for using the CRUSADE score for the entire study population is the absence of well-established bleeding risk scores for STEMI patients, as acknowledged in the 2017 ESC STEMI Guidelines. Furthermore, the CRUSADE score was easier to calculate in comparison with other scores since its variables were all available in the dataset. We have acknowledged this limitation in our manuscript as per your suggestion (quoted below and added in the manuscript).

“Finally, the CRUSADE score has been originally designed and validated for patients with NSTEMI. Therefore, it may over or underestimate bleeding risk in those with STEMI, although it previous studies have found it to be reliable in estimating bleeding risk in this population.”

Reference: Ariza-Solé A, et al. CRUSADE bleeding risk score validation for ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Thromb Res.* 2013;132(6):652-8. doi: 10.1016/j.thromres.2013.09.019. Epub 2013 Sep 26. PMID: 24112751.

Response to Editorial and Reviewers' comments

Editor's comments:

The authors should be commended for their efforts in conducting this investigation.

The study is of interest with a relevant sample size.

In order to harmonize the study, I would strongly suggest to divide the population in three groups: LOW-LOW (about 100000 patients), HIGH-HIGH (About 200000) and all remaining patients (intermediate group with about 300000 patients). This could facilitate statistics and improve the readability of the manuscript, making easier the evaluation of gender difference in outcome across the three groups and the comparison between the three groups in terms of baseline characteristics and outcome.

Response: We thank the editor for their comment and fully agree that this would further simplify matters. We have, therefore, decided to reclassify our cohort as per this suggestion and have updated the results accordingly.

Reviewer #1:

The study presented in this manuscript aimed to identify the gender differences in the managements and outcomes of hospitalized ACS patients with different combined bleeding-ischemic risk. Clinical data of 584 360 hospitalized patients with ACS in the United Kingdom from 2010-2017 were retrospectively analyzed. The ACS patients were divided into 9 combined bleeding-ischemic risk groups according different combinations of low, medium and high risk by the CRUSADE and GRACE scores. Based on the descriptions of this manuscript, the study found about one third of the ACS patients were classified as dual high-risk group in both men and women. In comparison to the dual low-risk group, the dual high-risk patients of both sexes were less likely to receive coronary angiography (CA), PCI, and DAPT and had much higher risks for MACE, all-cause death, cardiac death and bleeding during hospitalization. Compared with male patients with the same risk, female patients with the dual-high risk received less PCI and DAPT treatments, were more likely to experience MACE, all-cause and cardiac mortality. The study therefore concluded that female are less likely to receive guideline-recommended therapy and experience significantly worse outcomes. The main research questions are clinically relevant and important, and the results may reflect the problems or challenges in the management of ACS inpatients for men and women. But several issues need to further clarify.

My comments are in below.

1. If the study aimed to compare and assess the gender differences in performance for guidelines recommended managements of ACS with different bleeding-ischemic risk, it is better to recruited only ACS patients under 75 years old or add stratified analyses by age because the most evidence for PCI, DAPT came from RCTs included none or very small proportion patients over 75 years old and the main guidelines recommendations for the management of ACS inpatients may not suitable for patients with very old age. I think the substantial differences in utilities of CA, PCI and DAPT treatments and the MACE, in-hospital mortalities and bleeding between dual high-risk group and dual low-risk

group, and between men and women identified by this study can be largely explained by the significant differences in age among the risk groups and between men and women. While the mean ages in dual high-risk group were 77 ± 10 in men and 82 ± 10 in women, the mean ages in dual low-risk group were 54 ± 10 in men and 57 ± 10 in women. The Group 3 and group 6 had higher mean ages than group 1,2,4,5,7 and 8. And women in group 3 and group 6 and group 9 had much high mean age than men in the same groups.

Response: We thank the reviewer for their comment. Indeed, elderly patients are either excluded or underrepresented in many trials, as is the case for women, but this is the reason why we are left with very limited outcomes data in this population and also a strength of our study. We believe that our findings reflect real-world practice, in which a significant proportion of patients are elderly. Age is only a single component of GRACE, and not even included in the CRUSADE score. Therefore, many patients will still be at a dual high-risk even if aged less than 75 years and age cannot solely explain our findings. Moreover, risk groups were compared to one another within the same sex, not across sexes (e.g. Low-Low vs. High-High within males, and separately for females) so the age difference between men and women has no influence on the findings reported. In order to further simplify our argument, we have performed a sensitivity analysis that only included patients aged less than 75 years (results below and included in the Supplementary Material). As the reviewer will note, the differences in crude rates of clinical outcomes as well as receipt of invasive management and DAPT between risk groups, and between sexes in the dual high-risk group, are very similar to those found in the original cohort.

Supplementary Table 2. In-hospital management strategy and outcomes (unadjusted) in patients aged <75 years

	Low GRACE- Low CRUSADE (n=96356)		All other risk combinations (n=217,223)		High GRACE-High CRUSADE (n=63,885)	
	M (73.0%)	F (27.0%)	M (73.6%)	F (26.4%)	M (79.9%)	F (20.1%)
CA, %	76.6	77.2	69.8	67.4	57.3	51.3
PCI, %	56.7	48.9	50.1	43.9	37.5	29.4
Primary PCI, %	28.9	19.4	36.5	31.1	35.8	22.9
CABG, %	3.0	2.0	3.5	2.4	3.8	2.8
PCI planned after discharge, %	2.1	1.9	2.1	1.8	1.6	1.5
CABG planned after discharge, %	2.5	1.6	2.9	1.9	3.0	2.0
MACE*	0.9	0.9	1.8	2.7	9.7	11.7
All-cause mortality, %	0.2	0.3	1.2	2.3	9.8	12.9
Cardiac mortality, %	0.2	0.3	1.0	1.9	8.6	10.9
Reinfarction, %	0.8	0.7	0.8	0.9	1.5	1.3
All-cause bleeding, %	1.0	1.2	1.3	1.8	2.7	3.5
TIMI major bleeding, %	0.2	0.2	0.3	0.3	0.6	0.5
Discharge Medications*						
ACEI, %	90.5	85.4	88.9	84.0	76.9	68.5
Beta-blockers, %	89.2	84.6	88.1	83.3	79.6	72.2
Statins, %	96.7	94.2	95.8	93.1	88.3	84.0
Antiplatelets, %						
None	1.3	2.1	1.6	2.2	3.2	4.7
Aspirin only	6.1	8.0	7.0	8.4	13.6	15.9
P2Y12 inhibitor only	1.9	2.7	2.4	3.5	4.1	5.7
DAPT	90.7	87.2	89.0	85.9	79.1	73.8

ACEI: angiotensin converting enzyme inhibitor; CA: coronary angiography; CABG: coronary artery bypass grafting; DAPT: dual antiplatelet therapy (aspirin and any P2Y12 inhibitor); PCI: percutaneous coronary intervention; TIMI: thrombolysis in myocardial infarction; MACE: major acute cardiac events (composite of cardiac mortality and reinfarction)

2. It is necessary for authors to provide information regarding missing rates of the key variables, especially those to calculate GRACE and CRUSADE score and those as outcomes, such as statuses of CA, PCI and DAPT uses. Even the multiple imputation has demonstrated less bias, it is not suitable for variables with high missing rates.

Response: Thank you, these have now been provided in Supplementary Table 1. The values were not missing at significant rate, but also not low enough to have justified exclusion as opposed to imputation.

3. Both primary PCI and early DAPT uses may lower the risks of MACE and in-hospital mortalities in these ACS patients. It is reasonable to add the two variables as potential confounders in the models to estimate the risk of the MACE and in-hospital mortality by different bleeding-ischemic risk groups in both men and women.

Response: Primary PCI would be collinear with PCI and, therefore, we cannot adjust for both. Furthermore, not all ACS cases would have required primary PCI, which is why we chose to include overall PCI instead. We have already adjusted for inpatient use of DAPT in our original submission (mentioned in the methods and quoted below) and have done so again in our reanalysis of the revised groups (Low-Low, High-High and all other risk groups) based on the editor's suggestion.

“Multiple logistic regression was used to examine the association between the combined CRUSADE-GRACE risk groups and clinical outcomes adjusting for the following variables: ethnicity, use of inpatient pharmacotherapy (inpatient DAPT, beta blockers and furosemide)”

4. Some information in Table 1 B is quite confused. It is not clear if the proportions of PCI (line 2) included also primary PCIs. If it is yes, why some proportions of PPCI were larger than the proportions of PCI (Group 3). And the proportions of CA should be larger than the proportions of PCI (or PCI+PPCI if the proportion of PCI did not include PPCI because all PCIs must be based on CA.

Response: We thank the reviewer for their comment. PCI also includes primary PCI. We understand that there was a slightly discrepancy in Group 3 as the reviewer has rightly noted and this was corrected. However, owing to the reclassification of study groups in to 3 instead of 9, as suggested by the editor, we have combined all the risk groups other than High-High and Low-Low in to one group for ease of presentation and interpretation by the wider readership.

5. There were some inconsistencies between data provided by Table 1 B and those by Figure 2A. From the Figure 2A, I found female patients with ACS in dual bleeding-ischemic risk group had higher use rates for CA, PCI and discharge DAPT than male patients in the same group in all time points. But in Table 1B, female patients with ACS in dual bleeding-ischemic risk group had lower mean use rates of CA, PCI and DAPT at discharge than male patients.

Response: We thank the reviewer for their comment. The data in Table 1B is correct and we have double checked this. However, there was a discrepancy in the axis scales/labelling in the figures and this has been corrected in Figure 2A.

6. I didn't find Table 2 and all supplementary Tables and figures in the manuscript.

Response: We thank the reviewer for their comment. All tables and supplementary material have been submitted with the initial submission but we apologise if any technical issues have not allowed you to see them. Furthermore, these files are usually checked by the editorial office before they reach reviewers, as is our experience when we review for IJC. We hope that all the material if available for you to kindly review this time round.

Reviewer #2

The manuscript for review provided the data on sex-based differences in the management and outcomes of ACS patients according to combined ischemic-bleeding risk.

The Authors performed a retrospective analysis of over 580 000 patients comprising all ACS hospitalizations in the UK between 2010 and 2017 (MINAP Project). They analyzed the distribution of ischemic (GRACE Risk Score) and bleeding risk (CRUSADE Bleeding Risk Score) between sexes and compared the adherence to the ESC guidelines and clinical outcomes. They revealed the variations in clinical characteristics, management strategies and outcomes with regard to ischemic-bleeding risk combinations. The Authors demonstrated that high GRACE risk groups were more prevalent in males than females and were less frequently treated invasively and with DAPT, especially females. This

group had worse clinical outcomes, particularly females. Dual high (CRUSADE and GRACE) group was associated with worse adherence to the guideline-recommended therapy and had significantly higher MACE and mortality. It was particularly evident in females.

The study concerns an important and clinically relevant topic. It is based on a very large nationwide ACS patient population. The results of a comprehensive analysis are clearly presented and discussed. Complex statistical tools have been applied. The study has a value of novelty. The manuscript is very well and interestingly written.

I have only one remark. The CRUSADE Bleeding Risk Score is dedicated to the NSTEMI-ACS population. Its application in STEMI patients would require some explanations and might be added to the limitations of this study.

Response: We thank the reviewer for their thorough appraisal of our manuscript for their valuable comments. We fully agree that the CRUSADE score was validated for NSTEMI-ACS population, although several studies have demonstrated its validity in the STEMI population as well (example reference below). Our rationale for using the CRUSADE score for the entire study population is the absence of well-established bleeding risk scores for STEMI patients, as acknowledged in the 2017 ESC STEMI Guidelines. Furthermore, the CRUSADE score was easier to calculate in comparison with other scores since its variables were all available in the dataset. We have acknowledged this limitation in our manuscript as per your suggestion (quoted below and added in the manuscript).

“Finally, the CRUSADE score has been originally designed and validated for patients with NSTEMI. Therefore, it may over or underestimate bleeding risk in those with STEMI, although it previous studies have found it to be reliable in estimating bleeding risk in this population.”

Reference: Ariza-Solé A, et al. CRUSADE bleeding risk score validation for ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Thromb Res.* 2013;132(6):652-8. doi: 10.1016/j.thromres.2013.09.019. Epub 2013 Sep 26. PMID: 24112751.

Highlights

- First nationwide study to examine receipt of guideline-recommended therapy for ACS according to sex and dual bleeding-ischemic risk group
- One in three males and females are at a dual high-risk of bleeding and ischemia
- Females are less likely to receive guideline-recommended therapy and experience significantly worse outcomes.
- A gap in evidence remains regarding optimal strategies for this dual high-risk group, especially among females who experience worse outcomes.

Abstract

Background: Risk factors for further bleeding and ischemic events after acute coronary syndrome (ACS) often overlap. Little is known about sex-based differences in the management and outcomes of ACS patients according to their combined bleeding-ischemic risk.

Methods: All ACS hospitalizations in the United Kingdom (2010-2017) were retrospectively analyzed, stratified by sex and bleeding-ischemic risk combination (using CRUSADE and GRACE scores). Multivariable logistic regression was performed to examine association between risk-groups and 1) receipt of guideline-recommended management and 2) in-hospital outcomes.

Results: Of 584,360 patients, a third of males (32.3%) and females (32.6%) were in the dual high-risk group (High CRUSADE- High GRACE). In comparison to the dual low-risk group (Low CRUSADE-Low GRACE), the dual high-risk patients of both sexes were 59-83% less likely to receive inpatient revascularisation (PCI or CABG) and 50% less likely to receive dual antiplatelet therapy (DAPT) on discharge, with a significant increase in odds of MACE (~8 to 9-fold), all-cause and cardiac mortality (25 to 35-fold), and bleeding (78-91%). The greatest difference in management and clinical outcomes between sexes was found in the dual-high risk group where females were less likely to receive guideline-recommended therapy (revascularisation and DAPT), compared to males, and were more likely to experience MACE, all-cause and cardiac mortality.

Conclusion: ACS patients with dual high-risk for bleeding and recurrent ischemia, especially females, are less likely to receive guideline-recommended therapy and experience significantly worse outcomes. Novel strategies are needed to effectively manage this highly prevalent, complex patient group and address the under-treatment of females.

Sex differences in distribution, management and outcomes of combined ischemic-bleeding risk following acute coronary syndrome

Brief title: ACS sex differences in ischemic-bleeding risk

Mohamed O. Mohamed, MRCP (UK)^{1,2}, Muhammad Rashid, PhD¹, Adam Timmis³, Sarah Clarke⁴, Claire Lawson⁵, Erin D. Michos, MD, MHS⁶, Chun Shing Kwok, MRCP (UK)¹, Mark De Belder⁷, Marco Valgimigli, MD, PhD⁸, Mamas A. Mamas, DPhil^{1,2}

(1) Keele Cardiovascular Research Group, Institutes of Applied Clinical Science and Primary Care and Health Sciences, Keele University, Stoke-on-Trent, United Kingdom

(2) Department of Cardiology, Royal Stoke Hospital, University Hospital North Midlands, Stoke-on-Trent, United Kingdom

(3) Department of Cardiology, Barts Heart Centre, Queen Mary University London, United Kingdom

(4) Department of Cardiology, Royal Papworth Hospital NHS Foundation Trust, Cambridge, United Kingdom

(5) Real World Evidence Unit, Diabetes Research Centre, University of Leicester, UK

(6) Division of Cardiology, Johns Hopkins Ciccarone Center for the Prevention of Cardiovascular Disease, Maryland, United States

(7) National Institute for Cardiovascular Outcomes Research, Barts Health NHS Trust, London, United Kingdom

(8) Department of Cardiology, Inselspital, Universitätsspital Bern, Bern, Switzerland

Correspondence to:

Prof. Mamas A. Mamas
Centre for Prognosis Research,
Institute of Primary Care and Health Sciences,
Keele University,
Stoke-on-Trent, ST5 5BG, UK

Word count (inc. title page, abstract and references): 5031

Word count (excluding title page, abstract and references): 3021

Key Words: GRACE, CRUSADE, risk scores, outcomes, management, sex

Introduction

Acute coronary syndromes (ACS) are the leading cause of mortality worldwide [1-3], with outcomes that have improved through the use of potent antithrombotic therapies and percutaneous coronary intervention (PCI). [4-7] Current guidelines recommend the use of validated risk scores to predict the risk of future ischemic and bleeding complications, and to guide invasive management in patients presenting with ACS. [8, 9] The Global Registry of Acute Coronary Syndrome (GRACE) risk score is the most commonly used in clinical practice and has been shown to predict the risk of further ischemic events and mortality in patients with ACS. [10] Several predictors included in the GRACE score overlap with the Can Rapid Risk Stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines (CRUSADE) score, which predicts the risk of in-hospital bleeding after ACS, including heart failure, blood pressure, heart rate and renal function, albeit with different contributing weights to either score. [11] Although current guidelines provide clear recommendations on the management of patients with a high risk of either further ischemia or future bleeding, a significant proportion of patients encountered in real-world practice are at a 'dual high-risk' of bleeding and ischemia, for whom the guidance on optimal management strategy is less clear. [8, 9, 12, 13] There are limited data on how risks of bleeding and recurrent ischemic events distribute between females and males and whether there are associated inequalities in management.

The present study was designed to examine differences in the distribution of ischemic and bleeding' risk between sexes in a national cohort of ACS hospitalizations in the United Kingdom (UK), and compare their receipt of guideline-based care and clinical outcomes over a seven-year period.

Methods

MINAP Dataset

The Myocardial Ischaemia National Audit Project (MINAP) collects prospective data on the management of ACS in England, Wales and Northern Ireland. [14] The dataset includes 123 variables detailing patient and procedural characteristics, processes of care and clinical outcomes, including in-hospital mortality and bleeding, from the time a patient seeks medical help up to the point of discharge and referral for rehabilitation.

Study Design and Population

All patients with a confirmed discharge diagnosis of ACS between January 2010 and December 2017 in the MINAP registry were included. All cases with an ‘undetermined’ or non-ACS diagnosis on discharge were excluded, as were those who received thrombolysis. A flow chart of the study exclusions is presented in **Supplementary Figure 1** (Supplemental material). Data was missing for several variables necessary for the computation of GRACE 2.0 and CRUSADE scores using the previously published variables and coefficients (frequencies listed in **Supplementary Table 1**). [10, 11] We performed multiple imputation analysis for all missing variables, which generated ten imputed datasets. All analyses were performed in each imputed dataset separately and then pooled using Rubin’s Rules. [15] Patients with missing outcome variables were excluded from the analysis of that outcome only (i.e. we did not impute outcomes). Multiple imputation has demonstrated minimal bias in previous publications. [16, 17]

The GRACE score was used to stratify patients in to three categories according to in-hospital mortality score: low (NSTEMI: 1-108, STEMI: 49-125), intermediate (NSTEMI: 109-140, STEMI: 126-154) and high (NSTEMI: 141-372, STEMI: 155-319). [10] CRUSADE score stratifies patient into 5 categories according to bleeding risk: very low (≤ 20), low (21-30), moderate (31-40), high (41-50) and very high (> 50). [11]

For the purpose of combined GRACE and CRUSADE analysis, we reclassified the CRUSADE groups into three categories by merging 'Very Low-' and 'Low-' risk groups into a 'Low' risk category and 'High-' and 'Very High-' risk groups into a 'High'- risk category to facilitate analysis by allowing an equal number of bleeding and ischemic risk group combinations. Patients were subsequently grouped into 3 risk profiles based on combined CRUSADE and GRACE risk groups: Low CRUSADE-Low GRACE, High CRUSADE-High GRACE 'dual high-risk group', and all other risk groups.

The primary outcome measures were in-hospital major acute cardiovascular events (MACE), in-hospital all-cause mortality and in-hospital all-cause bleeding. MACE was defined as a composite of in-hospital cardiac death and re-infarction. All-cause bleeding was defined as any clinically evident bleeding and drop in hemoglobin as coded in the MINAP dataset (any bleeding with fall in Hb of <30g/L, 30-50g/L or >50g/L, 'intracranial bleeding' and 'retroperitoneal hemorrhage'). The secondary outcome was the utilization of guideline-recommended therapy, namely the rate of receipt of coronary angiography, inpatient revascularization (percutaneous coronary intervention (PCI) and coronary artery bypass graft surgery (CABG)), and dual antiplatelet therapy (DAPT).

Statistical Analysis

Statistical analysis was performed using SPSS version 26 (IBM Corp, Armonk, NY). Continuous variables were presented as means with standard deviation (SD) and compared using ANOVA. Categorical variables were presented as frequencies and analyzed using the chi squared (X^2) test. Patients with missing endpoint variables were excluded from the analysis of that endpoint. Multiple logistic regression was used to examine the association between the combined CRUSADE-GRACE risk groups and clinical outcomes adjusting for the following variables: ethnicity, previous acute myocardial infarction (AMI) or angina, previous PCI, previous CABG, hypertension, hypercholesterolemia, previous cerebrovascular accidents, asthma or chronic obstructive pulmonary disease, smoking status, year of admission, admitting

consultant (Cardiologist vs. General physician) and use of inpatient pharmacotherapy (inpatient DAPT, beta blockers and furosemide) and receipt of inpatient revascularization (PCI and CABG) for all outcomes. Additionally, the following variables were adjusted for when analyzing MACE, death and bleeding outcomes but not receipt of treatment (coronary angiography, PCI and DAPT outcomes) as they were irrelevant to the latter: glycoprotein (GP) 2b/3a inhibitors, low molecular weight heparin (LMWH), fondaparinux, unfractionated heparin (UFH) and bivalirudin. Cases with in-hospital mortality were excluded prior to reporting performing multivariable regression models for examining the receipt of DAPT on discharge. Any covariates that were used to calculate either risk score (CRUSADE and/or GRACE) were not adjusted for to mitigate collinearity and multiple adjustment: age, sex, renal function, peripheral vascular disease, cardiac arrest on admission, diabetes mellitus, blood pressure, heart rate, hematocrit level, elevated troponin level, Killip Class and ST-segment deviation. All odds ratios (ORs) are adjusted and expressed as OR [95% confidence interval], unless otherwise specified.

Results

A total of 584,360 patients with ACS were admitted between 2010 and 2017 in the UK, of whom 390,340 (66.8%) were females. A lower proportion of females compared with males were found in the Low CRUSADE-Low GRACE and all other risk groups, but no difference in proportions of both sexes were observed in the dual high-risk group (**Figure 1A**).

Within all risk groups, females were older than males and less likely to present with STEMI than NSTEMI. (**Table 1A**) There was a higher prevalence of cardiovascular risk factors amongst females, including previous angina, peripheral vascular disease, diabetes, heart failure, chronic renal failure, hypertension and cerebrovascular disease. In comparison, males were more likely than females to have a positive smoking history, to have received prior PCI or CABG and to receive specialist care in the form of consultant cardiology review. In terms of inpatient

medications, females were more likely to receive furosemide, LMWH and fondaparinux, compared with males, and less likely to receive GP 2b/3a inhibitor, bivalirudin or a beta-blocker (Table 1A). There was no difference in the rate of DAPT prescription between the sexes except in dual high-risk group where females were less likely to receive DAPT compared with males (81.3% vs. 84.4%).

Receipt of guidelines recommended therapy

There was an inverse relation between increasing risk and receipt of invasive management (coronary angiography, PCI and CABG) and DAPT in both sexes. Under-treatment was particularly marked in the patients with dual High GRACE-High GRACE risk who were significantly less likely to receive invasive management (CA and revascularization) and DAPT throughout the study period compared with the Low GRACE-Low CRUSADE group (Table 1B and Figure 2A). Nevertheless, it was females in the High GRACE-High GRACE group who were most at risk of under-treatment, being significantly less likely than males to undergo coronary angiography (31.0% vs. 47.5%), in-hospital PCI (17.5% vs. 29.4%) and CABG (1.3% vs. 2.8%) and DAPT on discharge (65.2% vs. 73.6%) (Figure 1B). Similar findings were observed in a sensitivity analysis of patients aged <75 years. (Supplementary Table 2)

The lower rates of utilization in invasive management and DAPT in the High GRACE-High GRACE group compared to Low CRUSADE-Low GRACE patient was persistent in both sexes throughout the study period (Figures 2A, $p_{\text{trend}} < 0.001$ for all).

In multivariable analysis, patients of both sexes in the High GRACE-High GRACE group had the lowest odds of receipt of inpatient coronary angiography (females: OR 0.17, 95% CI 0.17, 0.18, males: OR 0.30, 95% CI 0.29, 0.31) and revascularisation (females: OR 0.33, 95% CI 0.32, 0.34, males: OR 0.41, 95% CI 0.40, 0.42), and DAPT on discharge (females: OR 0.50, 95% CI 0.48, 0.52, males: OR 0.51, 95% CI 0.49, 0.53) compared to patients in the Low GRACE-Low CRUSADE group (Table 2, Figure 2B).

Clinical outcomes

In both sexes, the rates of all-cause and cardiac mortality and recurrent myocardial infarction were highest in the in the High GRACE-High GRACE group compared to all other risk groups, especially the Low CRUSADE-Low GRACE group (**Table 2**). Within the High GRACE-High GRACE group, crude all-cause and cardiac mortality rates were significantly higher in females compared to males (16.0% vs. 11.7% and 13.5% vs. 9.9%, respectively), while the rate of all-cause bleeding was marginally higher in females than males (3.0% vs. 2.8%). However, the rates of TIMI major bleeding and reinfarction in the High GRACE-High GRACE group were similar between sexes (females vs. males: 0.5% vs. 0.6% and 1.5% each, respectively). (**Table 2**) The findings were similar in patients aged<75 years. (**Supplementary Table 2**)

In comparison to the Low CRUSADE-Low GRACE group, all risk groups, regardless of sex, were associated with increased adjusted odds of MACE, all-cause and cardiac mortality, and all-cause bleeding in multivariable analysis, with the highest odds observed in the High GRACE-High GRACE group. (**Table 2**) For males in the High GRACE-High GRACE group, odds (95% CI) of MACE, all-cause mortality, and cardiac mortality were 7.69 (7.07, 8.37), 33.62 (27.48, 38.71) and 34.80 (28.89, 41.91), respectively. (**Table 2, Figure 2B**) For females in the High GRACE-High GRACE group, odds (95% CI) of MACE, all-cause mortality, and cardiac mortality were 9.03 (7.91, 10.30), 25.61 (20.69, 31.70) and 27.42 (21.64, 34.74), respectively. The odds of all-cause bleeding in both males and females were higher in all risk-groups compared to the Low CRUSADE-Low GRACE groups, with the highest odds being in the dual high-risk group (females: OR 1.78 (1.56, 2.05); males: 1.91 (1.74, 2.09)). (**Table 2, Figure 2B**)

Discussion

The present study, for the first time, compares sex differences in combined ischemic-bleeding risk profile in a contemporary national cohort of more than half a million patients with ACS. Our main findings can be summarized in three points. First, we find that ischemic-bleeding risk combinations vary in their clinical characteristics, management strategies and subsequent

clinical outcomes. Second, we find that the ‘dual high-risk’ (High CRUSADE-High GRACE) group is highly prevalent, representing a third of ACS cases in both sexes, and was associated with less receipt of guideline-recommended therapy and significantly worse outcomes in both sexes compared to the dual low-risk (Low CRUSADE-Low GRACE) group, including an 8 to 9-fold increase in MACE and more than 25-fold increase in all-cause and cardiac-specific mortality. More importantly, within the dual high-risk group we observe further disparities between sexes where females were less likely to receive invasive management and DAPT compared to males, and experience higher rates of mortality but not reinfarction or all-cause bleeding.

Current society guidelines recommend the assessment of future ischemic and bleeding risks using validated risk scores such as GRACE (Class I, Level A) and CRUSADE (Class IIb, Level B), respectively, to guide the management of ACS. [8, 9, 13] These guidelines also provide algorithms for the duration and type of antiplatelet therapy based on predicted ischemic and bleeding risk and consider these as separate entities. However, many patients share risk factors for both ischemia and bleeding, placing them at a ‘dual high-risk’ for either event, emphasizing the importance of combined ischemic-bleeding risk assessment. However, guidelines do not provide recommendations on how patients at high risk of both ischemic and major bleeding complications should be managed. Indeed, several factors included in the GRACE score such as increasing age, kidney disease, signs of heart failure on presentation, heart rate and systolic blood pressure are also known predictors of increased bleeding. [11, 18] This dual high-risk group is highly prevalent, accounting for one in three ACS presentations, and poses a therapeutic challenge for physicians due to limited evidence around their optimal management strategy. While current guidelines recommend an early invasive management strategy in patients with high GRACE score (>140), the peri-procedural use of antithrombotic therapy, including potent anti-platelet agents, increases the risk of bleeding in this high-risk group. [8, 9, 13, 19-22] Therefore, a cautious approach involving simultaneous assessment of

bleeding and ischemic risk is required.

Sex differences in the presentation, management and clinical outcomes of ACS, have been previously reported. [23-27] Traditionally, the lower rates of utilization of invasive management in females have been attributed to differences in their baseline risk for further bleeding and ischemia compared to males. Sex is part of the CRUSADE score but not the GRACE score. Simultaneous assessment of bleeding and ischemic risks of different combined ischemic-bleeding risk profiles demonstrates that females were generally less likely to belong to the dual low-risk group, compared to males, but there was no difference in ‘dual high-risk’ distribution between sexes, which represented a third of all ACS cases in both sexes. Despite the latter, there was an inverse relationship between combined ischemic-bleeding risk category and receipt of invasive management and DAPT in both sexes, where patients in the dual high-risk group were 59-83% less likely to receive diagnostic coronary angiography or invasive revascularization (PCI or CABG), and 50% less likely to receive DAPT on discharge. Further, the rate of utilization of these strategies was significantly lower in females compared to males. These findings are likely due to physicians’ preference for a conservative management strategy in this group to avoid commitment to long-term DAPT in the case of PCI, [28] although there is emerging evidence to support short-term DAPT in high bleeding risk patients, regardless of complexity of their PCI procedure.[29] However, these concerns do not justify differences in receipt of guideline-recommended therapy between sexes of the same combined risk group. Our analysis shows that dual high-risk patients of both sexes are 78-91% more likely to experience in-hospital all-cause bleeding, compared to the dual low-risk group, but there was no difference in TIMI major bleeding between combined risk groups in both sexes. On the other hand, patients in the dual high-risk group were 25-35 times more likely to experience all-cause and cardiac mortality, and this finding was similar in both sexes. This would suggest that at early timepoints, ischemic events may be more important than major bleeding in this high ischemic, high bleeding cohort and that an invasive strategy may be the optimal approach given the high rate of ischemic

events. Equally, bleeding risk prediction may be more important at the time of hospital discharge to decide upon DAPT duration.

Based on our findings, deviation from guideline-recommended therapy in patients with a dual high-risk of bleeding and ischemia, including the use of invasive management and DAPT, does not reduce their overall risk of adverse outcomes. However, these findings need further validation through prospective studies with longer follow-up duration. The present findings carry great significance by highlighting disparities in receipt of guideline-recommended therapy and subsequent outcomes of ACS, even between sexes within the same combined bleeding-risk category. Moreover, they emphasize the importance of individualized management strategies in this complex dual high ischemic-bleeding risk population. Several options currently exist for managing this special group, including the use of clopidogrel instead of more potent P2Y₁₂ inhibitors and drug coated or drug-eluting stent platforms that requiring a shorter DAPT duration (e.g. 1 month) such as the Biofreedom™ DCS1 and Resolute Onyx stents, although the long-term efficacy of these strategies is yet to be established. [30, 31] [32] [33] Furthermore, the efficacy and safety of shorter DAPT regimens compared to conventional DAPT duration remains under investigation.[34]

Limitations

There are several limitations to the present study. Although the MINAP database captures a wide range of admission-related information, specific information regarding outcomes rely on the accuracy of data inputted by staff. Furthermore, certain angiographic and procedure-related findings in the intervention group are not captured (e.g. type and site of lesion, and number of arteries stented). Furthermore, our data only capture in-hospital outcomes and it is possible that long-term follow-up will demonstrate a greater difference in outcomes between combined risk-groups. Finally, the CRUSADE score has been originally designed and validated for patients with NSTEMI. Therefore, it may over or underestimate bleeding risk in those with STEMI, although it previous studies have found it to be reliable in estimating bleeding risk in

this population. [35]

Conclusion

In a national analysis of ACS hospitalizations, we demonstrate that one in three males and females are at a dual high-risk of bleeding and ischemia. Dual high-risk patients are less likely to receive guideline-recommended therapy, in the form of PCI and DAPT, and are associated with significantly worse outcomes, especially in females. Although our findings emphasize the importance of an individualized approach to the management of dual high-risk patients presenting with ACS, they also highlight the gap in current evidence on optimal strategies for managing this highly prevalent risk group, especially among females who remain more disadvantaged compared to males.

Funding

The authors have no funding disclosures to report.

References

- [1] Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. *N Engl J Med*. 2010;362:2155-65.
- [2] Recent hospitalization trends for acute myocardial infarction in Beijing. *Eur Heart J*. 2016;37:3188-9.
- [3] Roger VL. Epidemiology of myocardial infarction. *Med Clin North Am*. 2007;91:537-52; ix.
- [4] Rogers WJ, Canto JG, Barron HV, Boscarino JA, Shoultz DA, Every NR. Treatment and outcome of myocardial infarction in hospitals with and without invasive capability. Investigators in the National Registry of Myocardial Infarction. *J Am Coll Cardiol*. 2000;35:371-9.
- [5] Rogers WJ, Frederick PD, Stoehr E, Canto JG, Ornato JP, Gibson CM, et al. Trends in presenting characteristics and hospital mortality among patients with ST elevation and non-ST elevation myocardial infarction in the National Registry of Myocardial Infarction from 1990 to 2006. *Am Heart J*. 2008;156:1026-34.
- [6] De Luca L, Olivari Z, Bolognese L, Lucci D, Gonzini L, Di Chiara A, et al. A decade of changes in clinical characteristics and management of elderly patients with non-ST elevation myocardial infarction admitted in Italian cardiac care units. *Open Heart*. 2014;1:e000148.
- [7] Puymirat E, Simon T, Cayla G, Cottin Y, Elbaz M, Coste P, et al. Acute Myocardial Infarction: Changes in Patient Characteristics, Management, and 6-Month Outcomes Over a Period of 20 Years in the FAST-MI Program (French Registry of Acute ST-Elevation or Non-ST-Elevation Myocardial Infarction) 1995 to 2015. *Circulation*. 2017;136:1908-19.
- [8] Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with

ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018;39:119-77.

[9] Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Jr., Ganiats TG, Holmes DR, Jr., et al. 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;64:e139-e228.

[10] Fox KA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van de Werf F, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *Bmj*. 2006;333:1091.

[11] Subherwal S, Bach RG, Chen AY, Gage BF, Rao SV, Newby LK, et al. Baseline risk of major bleeding in non-ST-segment-elevation myocardial infarction: the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines) Bleeding Score. *Circulation*. 2009;119:1873-82.

[12] Mohamed MO, Kinnaird T, Anderson R, Rashid M, Martin GP, Freeman P, et al. Combinations of bleeding and ischemic risk and their association with clinical outcomes in acute coronary syndrome. *International Journal of Cardiology*. 2019;290:7-14.

[13] Roffi M, Patrono C, Collet J-P, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *European Heart Journal*. 2016;37:267-315.

[14] Wilkinson C, Weston C, Timmis A, Quinn T, Keys A, Gale CP. Cohort profile: the Myocardial Ischaemia National Audit Project (MINAP). *European Heart Journal - Quality of Care and Clinical Outcomes*. 2019.

[15] Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. : John Wiley & Sons Inc., New York; 1987.

[16] Cattle BA, Baxter PD, Greenwood DC, Gale CP, West RM. Multiple imputation for completion of a national clinical audit dataset. *Stat Med*. 2011;30:2736-53.

[17] Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *Bmj*. 2009;338:b2393.

[18] Lindholm D, Sarno G, Erlinge D, Svennblad B, Hasvold LP, Janzon M, et al. Combined association of key risk factors on ischaemic outcomes and bleeding in patients with myocardial infarction. *Heart*. 2019;105:1175-81.

[19] De la Torre Hernández JM, Sadaba Sagredo M, Telleria Arrieta M, Gimeno de Carlos F, Sanchez Lacuesta E, Bullones Ramírez JA, et al. Antithrombotic treatment during coronary angioplasty after failed thrombolysis: strategies and prognostic implications. Results of the RESPIRE registry. *BMC Cardiovasc Disord*. 2017;17:212-.

[20] Bittl JA, Baber U, Bradley SM, Wijeyesundera DN. Duration of Dual Antiplatelet Therapy: A Systematic Review for the 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2016;68:1116-39.

[21] Sharma A, Lavie CJ, Sharma SK, Garg A, Vallakati A, Mukherjee D, et al. Duration of Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation in Patients With and Without Acute Coronary Syndrome: A Systematic Review of Randomized Controlled Trials. *Mayo Clinic Proceedings*. 2016;91:1084-93.

[22] Lewis SR, Pritchard MW, Schofield-Robinson OJ, Alderson P, Smith AF. Continuation versus discontinuation of antiplatelet therapy for bleeding and ischaemic events in adults undergoing non-cardiac surgery. *Cochrane Database Syst Rev*. 2018;7:Cd012584.

- [23] Graham G. Acute Coronary Syndromes in Women: Recent Treatment Trends and Outcomes. *Clin Med Insights Cardiol.* 2016;10:1-10.
- [24] Bugiardini R, Ricci B, Cenko E, Vasiljevic Z, Kedev S, Davidovic G, et al. Delayed Care and Mortality Among Women and Men With Myocardial Infarction. *J Am Heart Assoc.* 2017;6:e005968.
- [25] Gupta T, Kolte D, Khera S, Agarwal N, Villablanca PA, Goel K, et al. Contemporary Sex-Based Differences by Age in Presenting Characteristics, Use of an Early Invasive Strategy, and Inhospital Mortality in Patients With Non-ST-Segment-Elevation Myocardial Infarction in the United States. *Circ Cardiovasc Interv.* 2018;11:e005735.
- [26] Gale CP, Cattle BA, Woolston A, Baxter PD, West TH, Simms AD, et al. Resolving inequalities in care? Reduced mortality in the elderly after acute coronary syndromes. The Myocardial Ischaemia National Audit Project 2003-2010. *Eur Heart J.* 2012;33:630-9.
- [27] Jneid H, Fonarow GC, Cannon CP, Hernandez AF, Palacios IF, Maree AO, et al. Sex differences in medical care and early death after acute myocardial infarction. *Circulation.* 2008;118:2803-10.
- [28] Valgimigli M, Bueno H, Byrne RA, Collet J-P, Costa F, Jeppsson A, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *European Heart Journal.* 2017;39:213-60.
- [29] Costa F, Van Klaveren D, Feres F, James S, Räber L, Pilgrim T, et al. Dual Antiplatelet Therapy Duration Based on Ischemic and Bleeding Risks After Coronary Stenting. *Journal of the American College of Cardiology.* 2019;73:741-54.
- [30] Urban P, Meredith IT, Abizaid A, Pocock SJ, Carrié D, Naber C, et al. Polymer-free Drug-Coated Coronary Stents in Patients at High Bleeding Risk. *New England Journal of Medicine.* 2015;373:2038-47.
- [31] Gerber Robert T, Arri Satpal S, Mohamed Mohamed O, Dhillon G, Bandali A, Harding I, et al. Age is not a bar to PCI: Insights from the long- term outcomes from off- site PCI in a real- world setting. *Journal of Interventional Cardiology.* 2017;30:347-55.
- [32] Waksman R, Piegari GN, Kabour A, Cannon L, Wang J, Adams G, et al. Polymer-free Biolimus A9-coated stents in the treatment of de novo coronary lesions with short DAPT: 9-month angiographic and clinical follow-up of the prospective, multicenter BioFreedom USA clinical trial. *Cardiovasc Revasc Med.* 2017;18:475-81.
- [33] Kedhi E, Latib A, Abizaid A, Kandzari D, Kirtane AJ, Mehran R, et al. Rationale and design of the Onyx ONE global randomized trial: A randomized controlled trial of high-bleeding risk patients after stent placement with 1month of dual antiplatelet therapy. *Am Heart J.* 2019;214:134-41.
- [34] Frigoli E, Smits P, Vranckx P, Ozaki Y, Tijssen J, Jüni P, et al. Design and rationale of the Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated Versus Standard DAPT Regimen (MASTER DAPT) Study. *American Heart Journal.* 2019;209:97-105.
- [35] Ariza-Solé A, Sánchez-Elvira G, Sánchez-Salado JC, Lorente-Tordera V, Salazar-Mendiguchía J, Sánchez-Prieto R, et al. CRUSADE bleeding risk score validation for ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Thromb Res.* 2013;132:652-8.

Figure titles and legends:

Figure 1A. Distribution of combined CRUSADE-GRACE risk groups according to sex

Figure 1B. In-hospital invasive management of dual high bleeding-ischemic risk group according to sex

Legend: CA: Coronary angiography; CABG: coronary artery bypass graft surgery; PCI: percutaneous coronary intervention; PPCI: primary PCI.

Figure 2A. Trends of receipt of invasive management and discharge DAPT in both sexes (2010-2017)

Legend: DAPT: dual antiplatelet therapy, composite of aspirin and any P2Y12 inhibitor; PCI: percutaneous coronary intervention

Figure 2B. Adjusted odds ratios (OR) and 95% confidence intervals of in-hospital invasive management and outcomes in the combined CRUSADE-GRACE groups*

Legend:

*Reference group is Low CRUSADE-Low GRACE group for each outcome

** Include inpatient PCI and CABG

CA: coronary angiography; DAPT: dual antiplatelet therapy, composite of aspirin and any P2Y12 inhibitor; MACE: Major adverse cardiac events (composite of cardiac mortality and re-infarction); PCI: percutaneous coronary intervention

Sex differences in management and outcomes of ACS according to combined bleeding-ischemic risk assessment

Combined CRUSADE + GRACE assessment

One in three males and females are high bleeding, high ischemic in risk

MANAGEMENT

High bleeding, high ischemic groups significantly less likely to receive inpatient CA (70-83% ↓ odds), revascularisation (PCI/CABG; 59-67% ↓ odds) and DAPT (~50% ↓ odds), especially in ♀

CLINICAL OUTCOMES

↑ ↑ adjusted odds of MACE (8-fold), all-cause and cardiac mortality (30 to 40-fold) in high bleeding, high ischemic (vs. dual low-risk) group with worse outcomes in ♀ compared to ♂

↑ 78-91% all-cause bleeding in both ♀ and ♂ in high bleeding, high ischemic group.

CA: coronary angiography; CABG: coronary artery bypass graft surgery; DAPT: dual antiplatelet therapy; PCI: percutaneous coronary intervention

Dual High-risk Group

[Click here to access/download](#)

Table

Table 1A.docx

[Click here to access/download](#)

Table

Table 1B.docx

[Click here to access/download](#)

Table
Table 2.docx

CRedit statement

Mohamed O. Mohamed: Methodology, Data curation, Formal Analysis, Writing- Original draft preparation, Visualisation; **Muhammad Rashid:** Writing- Reviewing and Editing, **Adam Timmis:** Writing- Reviewing and Editing, **Sarah Clarke:** Writing- Reviewing and Editing, **Claire Lawson:** Writing- Reviewing and Editing, **Erin D. Michos:** Writing- Reviewing and Editing, **Chun Shing Kwok:** Writing- Reviewing and Editing, **Mark De Belder:** Writing- Reviewing and Editing, **Marco Valgimigli:** Writing- Reviewing and Editing, **Mamas A. Mamas:** Conceptualization; Supervision; Writing- Reviewing and Editing

Author Agreement Form – International Journal of Cardiology

Manuscript Title: **Sex differences in distribution, management and outcomes of combined ischemic-bleeding risk following acute coronary syndrome**

List of all Authors: Mohamed O. Mohamed, Muhammad Rashid, PhD, Adam Timmis, Sarah Clarke, Claire Lawson, Erin D. Michos, Chun Shing Kwok, Mark De Belder, Marco Valgimigli, MD, PhD, Mamas A. Mamas, DPhil

Corresponding Author: Prof. Mamas A. Mamas

This statement is to certify that all authors have seen and approved the manuscript being submitted, have contributed significantly to the work, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission to the *International Journal of Cardiology*.

We attest that the article is the Authors' original work, has not received prior publication and is not under consideration for publication elsewhere. We adhere to the statement of ethical publishing as appears in the International of Cardiology (citable as: Shewan LG, Rosano GMC, Henein MY, Coats AJS. A statement on ethical standards in publishing scientific articles in the International Journal of Cardiology family of journals. *Int. J. Cardiol.* 170 (2014) 253-254 DOI:10.1016/j.ijcard.2013.11).

On behalf of all Co-Authors, the corresponding Author shall bear full responsibility for the submission. Any changes to the list of authors, including changes in order, additions or removals will require the submission of a new author agreement form approved and signed by all the original and added submitting authors.

All authors are requested to disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work. If there are no conflicts of interest, the COI should read: "The authors report no relationships that could be construed as a conflict of interest".

[Click here to access/download](#)

Supplementary Material

MINAP Sex differences Supplementary Material.docx