PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Admission glucose level and short-term mortality in older patients with acute myocardial infarction: results from the KORA myocardial infarction registry
AUTHORS	Mamadjanov, Temur; Volaklis, Konstantinos; Heier, Margit; Freuer, Dennis; Amann, Ute; Peters, Annette; Kuch, B; Thilo, Christian; Linseisen, Jakob; Meisinger, Christa

VERSION 1 – REVIEW

REVIEWER	Spanakis, Ilias University of Maryland School of Medicine
REVIEW RETURNED	08-Feb-2021

GENERAL COMMENTS	The current manuscript contains important information in a topic that has been however extensively studied. One of the strengths of the current study is that the authors evaluate the role of admission glucose values in older individuals. The authors have done laborious work and although the findings are not quite novel their findings deserve publication. My comments are: - About pathophysiology: The increased mortality that is seen in this study (but also in others) cannot be only related to the toxic effects of hyperglycemia or in generally secondary of hyperglycemia. The authors evaluated associations and not causality. Another explanation for example is that patients who were sicker-severely ill at admission had also hyperglycemia (as a result of the severity-stress of the illness). Therefore they died not because of the stress hyperglycemia or the hyperglycemia induced toxic effects but because of the underlying conditions. - One of the major limitations of the study is that the authors did not include major comorbidities. For example, they did not collect variables like COPD, CKD, history of amputations, peripheral vascular disease or other medical conditions which can increase the risk of death. The mortality can be significantly different among subjects who have underlying diseases. Authors should add this significant limitation in the discussion section as also remove it from the strengths (page 14) - Can the authors explain why the older group (75-84) had lower mortality? They should add this information in the discussion section. - Please change “diabetic” to patients with diabetes. The terminology diabetic is not accepted by the international diabetes organizations, as it may characterize inappropriately individuals with diabetes.

REVIEWER	Cheung, N Wah University of Sydney
REVIEW RETURNED	14-Feb-2021

GENERAL COMMENTS	This observational study reports on the association between admission glucose levels and outcomes of myocardial infarction in older patients. The paper is overall well written. A few comments: Can the authors please state clearly that diabetes status was based on what was known on admission only, if this was the case. If alternatively it includes cases diagnosed during the course then this should be stated. In the results the authors state that the observed associations are stronger for patients without diabetes and refer to table 4. However neither in table 4 nor in the text is there a statistical test which compares patients with diabetes vs patients without diabetes. In order to make this statement, it has to be demonstrated statistically. The investigators have highlighted that a novel aspect of the study is that there was no independent association between glucose and fatality amongst the older patients, and there is a lack of relationship between admission glucose and STEMI amongst the young old patients, and between glucose and NSTEMI among the older patients. A number of possible reasons for this are mentioned in the Discussion. However the most likely explanation is a lack of power. The direction of the effect is consistent for all the relationships between glucose and outcomes. Where mortality was not significant, hospital complications were significant. Where hospital complications were not significant, mortality was significant. Therefore it is likely that the association between glucose and AMI outcomes is likely to be there irrespective of age, and whether it is a STEMI or NSTEMI. If the authors accept this view, then the discussion and abstract will need to be modified to reflect this.

REVIEWER	Chattopadhyay, Sudipta Milton Keynes University Hospital, Cardiology
REVIEW RETURNED	14-Feb-2021

GENERAL COMMENTS	Major Comments There is nothing novel about this study. The adverse effect of diabetes on post-MI prognosis is well established. There is a large volume of literature demonstrating the adverse post-MI prognosis in patients without known diabetes and raised ABG. The authors cite Timmer et al in relation to ischemia-reperfusion injury but not their other outcome papers (Circulation. 2011;124 704-711, Am Heart J 2004;148 399-404) or Norhammar et at (Diabetes Care 1999;22:1827-31). The fact that increasing ABG in patients without known diabetes is associated with higher mortality irrespective of age is no different from the conclusion of several other previous studies. The conclusion paragraph is very confusing due to the use of the word “older”. The authors conclude that “High admission blood glucose (ABG) significantly increased the risk of short-term mortality and complications among older patients hospitalized with

	incident AMI independent of diabetes status." This is not quite so. The higher ABG is associated higher mortality irrespective of the diabetes status only in under-75 group. For the over-75 group it is only true for patients without diabetes. This needs clarification. The clinical significance of "admission hyperglycaemia" has always been very difficult to interpret. Several papers describe this as stress hyperglycaemia and associates it with poor prognosis. It has often been (mis)interpreted as "stress hyperglycaemia". Due to the difficulty in recognition (ABG level to be considered as abnormal has varied even in guidelines and position papers) and interpretation of admission hyperglycaemia, the concept of admission hyperglycaemia has long been superseded by the concept of "unrecognized diabetes" and "hospital-related hyperglycemia" as long ago as 2004. (Diabetes Care. 2004 Feb;27(2) 553-91). Recent consensus is that hyperglycaemia during a hospital admission cannot be interpreted without HbA1c to test for undiagnosed diabetes or prediabetes and post-discharge tests to assess whether the glycaemic state has normalised after stress of hospital admission has been removed. (Endocr Pract 2015;21 Suppl 1:1-87, Diabetes Care 2004;27:553-91) So, without these clarifications the clinical relevance of the current study is questionable. In the current study 62% had no known diabetes. How do the authors exclude the possibility that the events in this group are not driven by events in the undiagnosed diabetes and prediabetes in this group? The findings "underscore the importance of a close(ly) glycemic control during hospital stay particularly in certain subgroups of older AMI patients". What does that mean? Are they suggesting that any patient ≥65 years without diabetes have their blood glucose controlled irrespective of the ABG level as 1SD increase in ABG will increase mortality? Without a definition of "high" ABG, this information is clinically inapplicable and therefore irrelevant. In the mixed population (38% known diabetes) the median admission glucose was 94(70) mg/l [5.2(3.9) mmol/l]. Would any clinician even consider this as hyperglycaemia to act on it? Patients with "low" ABG have higher 30d-mortality than ones with normal (Circulation. 2011;124 704-711). How was missing data dealt with? No mention of imputation! 23% LVEF missing. 7% cardiac arrest missing. How was missing data managed? Why was multivariable analysis done rather than the conventional Cox proportional hazard analysis? The models would be considered weak in the absence of several variables that affect prognosis e.g. creatinine, LVEF and composite score like the GRACE. There is some suggestion that ABG significantly predicts prognosis in patients with known diabetes if it is included as the only glycaemic matrix in models but not when other glycaemic matrices are added and that mainly newly diagnosed DM, determined prognosis in patients with hospital related hyperglycaemia and imposed an additional prognostic risk. (J Diabetes Complications. 2020 Apr;34(4):107518. Acta Diabetol. 2018 May;55(5):449-458). So the ABG alone, without clarifying what this means in patients without known diabetes, is not clinically useful.

	Minor Comments Anticoagulants in the treatment of AMI?? Did they mean antiplatelets……….if so what? Line 16: it is Timmer not Trimmer! Ref 5: this ref is not formatted properly.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Ilias Spanakis, University of Maryland School of Medicine

Dear Dr. Spanakis, thank you for your valuable feedback on our mansucript. In the following, we respond to all your comments. The page numbers on which the changes can be found refer to the version with the track changes.

Comments to the Author:
The current manuscript contains important information in a topic that has been however extensively studied. One of the strengths of the current study is that the authors evaluate the role of admission glucose values in older individuals. The authors have done laborious work and although the findings are not quite novel their findings deserve publication. My comments are:

- About pathophysiology: The increased mortality that is seen in this study (but also in others) cannot be only related to the toxic effects of hyperglycemia or in generally secondary of hyperglycemia. The authors evaluated associations and not causality. Another explanation for example is that patients who were sicker-severely ill at admission had also hyperglycemia (as a result of the severity-stress of the illness). Therefore, they died not because of the stress hyperglycemia or the hyperglycemia induced toxic effects but because of the underlying conditions.

Response

Thank you for this comment. We agree that we evaluated associations and not causality. We discussed the issues mentioned by the reviewer in the limitations section and the conclusions (see pages 14 and 15).

Comment

- One of the major limitations of the study is that the authors did not include major comorbidities. For example, they did not collect variables like COPD, CKD, history of amputations, peripheral vascular disease or other medical conditions which can increase the risk of death. The mortality can be significantly different among subjects who have underlying diseases. Authors should add this significant limitation in the discussion section as also remove it from the strengths (page 14).

Response

Thank you for this hint. We modified our limitations section according to your suggestion. Furthermore, we removed the mentioned comorbidities from the strengths (see page 14).

Comment

- Can the authors explain why the older group (75-84) had lower mortality? They should add this information in the discussion section.

Response

Thank you for the comment. The 28-day case fatality in the age-group 75-84 years was significantly higher than in the age-group 65-74 years (see Table 3). The association between admission glucose levels and 28-day case fatality was non-significant in the older age-group. This result was now discussed on page 13, last paragraph and page 14, first paragraph.

Comment

- Please change “diabetic” to patients with diabetes. The terminology diabetic is not accepted by the international diabetes organizations, as it may characterize inappropriately individuals with diabetes.

Response

Thank you for the hint. We changed to “patients with diabetes” throughout the manuscript.

Reviewer: 2

Prof. N Wah Cheung, University of Sydney

Dear Prof. Wah, thank you for your comments and valuable feedback on our mansucript. In the following, we respond to all your comments. The page numbers on which the changes can be found refer to the version with the track changes.

Comments to the Author:

This observational study reports on the association between admission glucose levels and outcomes of myocardial infarction in older patients. The paper is overall well written.

A few comments:

Can the authors please state clearly that diabetes status was based on what was known on admission only, if this was the case. If alternatively, it includes cases diagnosed during the course then this should be stated.

Response

Thank you for this comment. We now clearly state, that diabetes status was based on what was known on admission only (see page 6, last paragraph).

Comment

In the results the authors state that the observed associations are stronger for patients without diabetes and refer to table 4. However, neither in table 4 nor in the text is there a statistical test which compares patients with diabetes vs patients without diabetes. In order to make this statement, it has to be demonstrated statistically.

Response

Thank you for the comment, you are correct. We have omitted this strong statement (see page 10, second paragraph).

Comment

The investigators have highlighted that a novel aspect of the study is that there was no independent association between glucose and fatality amongst the older patients, and there is a lack of relationship between admission glucose and STEMI amongst the young old patients, and between glucose and NSTEMI among the older patients. A number of possible reasons for this are mentioned in the Discussion. However, the most likely explanation is a lack of power. The direction of the effect is consistent for all the relationships between glucose and outcomes. Where mortality was not significant, hospital complications were significant. Where hospital complications were not significant, mortality was significant. Therefore, it is likely that the association between glucose and AMI outcomes is likely to be there irrespective of age, and whether it is a STEMI or NSTEMI. If the authors accept this view, then the discussion and abstract will need to be modified to reflect this.

Response

Thank you for this comment. In our analysis there was a significant association with age, thus, age can be considered as effect modifier; consequently, we stratified the analysis by age. We agree with the reviewer that the results for both age-groups after stratification were all in the same direction, but the association was only significant for the younger age-group regarding the outcome 28-day case fatality. Due to the large number of missing values presented in Table 1, we now used multiple imputation before regression as recommended by Reviewer 3. Since the missing mechanism was not completely at random, this approach minimized bias of the effect estimates and increased statistical power. Analyses with imputed data came to similar results.
We assume, that it is likely that admission glucose plays only a minor role in terms of case-fatality in higher-aged AMI patients (see comments from Reviewer 1). The older the patients are, the more comorbidities they may have and the sicker these patients may be when admitted to hospital. The probability that they die from these conditions is higher than that an increased admission glucose is the cause of death.
We have revised the abstract and manuscript accordingly and added some points in the discussion and conclusions section. We hope that the reviewer agrees with this interpretation of the results (see pages 2, 13-15).

Reviewer: 3

Dr. Sudipta Chattopadhyay, Milton Keynes University Hospital

Dear Dr. Chattopadhyay, thank you for reviewing our manuscript and your valuable comments on it. In the following, we respond to all your comments. The page numbers on which the changes can be found refer to the version with the track changes.

Comments to the Author:

Major Comments
There is nothing novel about this study. The adverse effect of diabetes on post-MI prognosis is well

established. There is a large volume of literature demonstrating the adverse post-MI prognosis in patients without known diabetes and raised ABG. The authors cite Timmer et al in relation to ischemia-reperfusion injury but not their other outcome papers (Circulation. 2011;124 704-711, Am Heart J 2004;148 399-404) or Norhammar et at (Diabetes Care 1999;22:1827-31). The fact that increasing ABG in patients without known diabetes is associated with higher mortality irrespective of age is no different from the conclusion of several other previous studies.

Response

We agree with the reviewer that there are a number of studies investigating this topic. However, studies focusing on older patients with myocardial infarction using real world data from a population-based myocardial infarction registry gathering the data from all patients without selection are not so common so far.
We have now added the publications mentioned by the reviewer in our manuscript (see Reference section, pages 17-19).

Comment

The conclusion paragraph is very confusing due to the use of the word "older". The authors conclude that "High admission blood glucose (ABG) significantly increased the risk of short-term mortality and complications among older patients hospitalized with incident AMI independent of diabetes status." This is not quite so. The higher ABG is associated higher mortality irrespective of the diabetes status only in under-75 group. For the over-75 group it is only true for patients without diabetes. This needs clarification.

Response

Thank you for this hint. We now revised the abstract and the conclusions section of the manuscript (see pages 2 and 15).

Comment

The clinical significance of "admission hyperglycaemia" has always been very difficult to interpret. Several papers describe this as stress hyperglycaemia and associates it with poor prognosis. It has often been (mis)interpreted as "stress hyperglycaemia". Due to the difficulty in recognition (ABG level to be considered as abnormal has varied even in guidelines and position papers) and interpretation of admission hyperglycaemia, the concept of admission hyperglycaemia has long been superseded by the concept of "unrecognized diabetes" and "hospital-related hyperglycemia" as long ago as 2004. (Diabetes Care. 2004 Feb;27(2) 553-91). Recent consensus is that hyperglycaemia during a hospital admission cannot be interpreted without HbA1c to test for undiagnosed diabetes or prediabetes and post-discharge tests to assess whether the glycaemic state has normalised after stress of hospital admission has been removed. (Endocr Pract 2015;21 Suppl 1:1-87, Diabetes Care 2004;27:553-91) So, without these clarifications the clinical relevance of the current study is questionable.

Response

Thank you for this comment. We have now included in the limitations section, that "In patients without diabetes, admission blood glucose alone without HbA1c values to test for undiagnosed diabetes or prediabetes and without post-discharge tests to assess the glycaemic state after the drop of stress during hospital admission, the meaning and interpretation of admission hyperglycaemia in clinical practice is difficult." (see also your comment below) (see page 14). We also added the references suggested by the reviewer (see Reference section, pages 17-19).

Comment

In the current study 62% had no known diabetes. How do the authors exclude the possibility that the events in this group are not driven by events in the undiagnosed diabetes and prediabetes in this group?

Response

Thank you for the comment. We cannot entirely exclude that patients with undiagnosed diabetes or prediabetes are included in the patients-group without diabetes. This is a limitation of the study and we discussed this point in our limitations section (see page 14).

Comment

The findings “underscore the importance of a close(ly) glycemic control during hospital stay particularly in certain subgroups of older AMI patients”. What does that mean? Are they suggesting that any patient ≥65 years without diabetes have their blood glucose controlled irrespective of the ABG level as 1SD increase in ABG will increase mortality? Without a definition of “high” ABG, this information is clinically inapplicable and therefore irrelevant. In the mixed population (38% known diabetes) the median admission glucose was 94(70) mg/l [5.2(3.9) mmol/l]. Would any clinician even consider this as hyperglycaemia to act on it? Patients with “low” ABG have higher 30d-mortality than ones with normal (Circulation. 2011;124 704-711).

Response

Thank you for this hint. We agree with the reviewer and have deleted this statement (see page 15, first paragraph).

Comment

How was missing data dealt with? No mention of imputation! 23% LVEF missing. 7% cardiac arrest missing. How was missing data managed?

Response

Thank you for this valuable comment. Due to the large number of missing values presented in Table 1, we now used multiple imputation before regression. Since the missing mechanism was not completely at random, this approach minimized bias of the effect estimates and increased statistical power. Altogether the results did not change when repeating the analyses after imputation (see page 7, last paragraph, and Table 4).

Comment

Why was multivariable analysis done rather than the conventional Cox proportional hazard analysis? The models would be considered weak in the absence of several variables that affect prognosis e.g. creatinine, LVEF and composite score like the GRACE. There is some suggestion that ABG significantly predicts prognosis in patients with known diabetes if it is included as the only glycaemic matrix in models but not when other glycaemic matrices are added and that mainly newly diagnosed DM, determined prognosis in patients with hospital related hyperglycaemia and imposed an additional prognostic risk. (J Diabetes Complications. 2020 Apr;34(4):107518. Acta Diabetol. 2018

May;55(5):449-458). So the ABG alone, without clarifying what this means in patients without known diabetes, is not clinically useful.

Response

Thank you. We conducted binary logistic regression models, because the days that passes before the event death occurred were not available. For the analyses, only the outcome 28-days survived (yes/no) was available. The reviewer is correct that we did not assess major comorbidities which can increase the risk of death (e.g. lung disease, chronic renal failure or peripheral vascular disease) and for this reason our results should be interpreted with caution. We added these points in the limitations section (see page 14).

We have now also included in the limitations section, that “In patients without diabetes, admission blood glucose alone without HbA1c values to test for undiagnosed diabetes or prediabetes and without post-discharge tests to assess the glycaemic state after the drop of stress during hospital admission, the meaning and interpretation of admission hyperglycaemia in clinical practice is difficult.” (see page 14). Furthermore, we now cite the references mentioned by the reviewer (see References section, pages 17-19).

Minor Comments

Anticoagulants in the treatment of AMI?? Did they mean antiplatelets………..if so what?

Response

Yes, we meant “antiplatelets” and replaced “anticoagulants” with “antiplatelets”.

Comment

Line 16: it is Timmer not Trimmer!

Response

Thank you. We corrected it.

Comment

Ref 5: this ref is not formatted properly.

Response

We have corrected it.

VERSION 2 – REVIEW

REVIEWER	Spanakis, Ilias University of Maryland School of Medicine
REVIEW RETURNED	19-May-2021

GENERAL COMMENTS	The authors addressed my comments and I think that the manuscript is suitable for publication

REVIEWER	Chattopadhyay, Sudipta Milton Keynes University Hospital, Cardiology
REVIEW RETURNED	11-May-2021

GENERAL COMMENTS	All the issues that I had raised have been satisfactorily dealt with. Please delete the word "infarction" after "STEMI" in Line 45 in the Results section of the Abstract.