PEER REVIEW HISTORY

This paper was submitted to the HEART but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Is blood glucose concentration a more powerful predictor of mortality after acute myocardial infarction than diabetes diagnosis? A retrospective cohort study
AUTHORS	Gholap, Nitin ; Mehta, Rajnikant; Ng, Leong; Davies, Melanie; Khunti, Kamlesh; Squire, Iain

VERSION 1 - REVIEW

REVIEWER	Weston, Clive Swansea University I have written articles concerning this clinical scenario. I sit on the MINAP Academic Group with the senior author of the this submission - we have not discussed the submission. I have co-authored a short editorial for Heart (in process of submission) that concerns the recent NICE guideline on management of hypreglycaemia during acute coronary syndrome.
REVIEW RETURNED	29-Mar-2012

GENERAL COMMENTS	In this observational study the authors' stated aim is to compare the relative strength of association (in STEMI and in nSTEMI) between outcome (death at 30 days and 1 year after index event) and two predictors - a prior diagnosis of diabetes mellitus and the 'admission' blood glucose concentration (more accurately, the first recorded laboratory-determined plasma glucose concentration) - when adjusted for other presumed or documented predictors. Their finding is that while both prior diabetes and higher levels of admission blood glucose are associated with poorer outcomes after heart attack, the association is much stronger for the absolute level of glucose, and when blood glucose is included in the predictive model the association with diagnosed diabetes is lost. In their model, which includes blood glucose, diabetes was not an independent predictor of moratlity after heart attack. This is true for STEMI and nSTEMI - though interestingly the association between mortality and glucose appears to diminish over the year. Abstract - Structured abstract. MINAP is Myocardial Ischaemia National Audit PROJECT rather than PROGRAMME. Introduction - Good well-referenced introduction. Clearly-stated aim in last paragraph. Methods - MINAP = project in para 1. Also suggest a more

	contemporary reference for the MINAP (Herrett E, Smeeth L, Walker L, Weston C. The Myocardial Ischaemia National Audit Project (MINAP) Heart 2010;96:1264-67) instead of the present ref 18. Were all patients with prior diagnosis of diabetes type 2 diabetic? Is it safe to assume that all 'admission' blood glucose measurements were performed on blood obtained within 12 hours of arrival at hospital, or before any treatment for hyperglycaemia was instigated? You have some information on in-hospital treatment - do you have any on specific treatment to reduce raised blood glucose? In my comments regarding study design I have stated: I do not feel that my personal expertise in statistics is sufficient to critique the statistical techniques used (eg. fractional polynominals) - though the description of, and rationale for, the 'stats' is good. Results - the dates in line 1 are 2002 until 2009. I think that this should be 2002-2008 (as in other sections of the paper). You have chosen to express plasma glucose as mean with standard deviation. Was there a normal distribution of values. What about medians (with IQR)? I got confused at the start of the section on 'Mortality - univariate analysis. I was expecting 4 numbers - for those dying during hospitalisation, within 30 days, within 1 year and over the whole period available for study. Instead there were only three. What was the number of those dying in hospital after the index event? It's 319 isn't it (4111-3792)? There are then slight discrepancies between the numbers reported to have died after discharge and those having diedafter the index event (eg all deaths up to 30 days = 409; deaths after discharge up to 30 days = 106 - so deaths in hospital 303 not 319). I guess that this must reflect different cuts of the data. How did you deal with missing data (particularly with missing glucose estimates)? Discussion - I would reword the first two sentences (eg "Both a prior diagnosis of diabetes and....This is the first study to compare the relative strengths of the association of .....) You say that you show no trend to increased assoc between diabetes and mortality after AMI. But in your univariate analysis (table 2) the HR goes from 1.4 at 30 days to 1.58 at 1 yr to 1.65 at 912 days. Even in multivariate analysis the HR increases albeit the 95% CI straddles 1.0. Is there no trend here? What if any effect would more aggresive treatment of raised blood glucose in those with prior diabetes have on your findings regarding the relative strengths of associations - there is evidence (kosiborod, MINAP annual report - you mention this in Discussion) that for any given level of admission blood glucose a person with diabetes is more likely to be given insulin. I think you are pushing it a little to use DIGAMI 2 (ref17) to support your statement that "active management of blood glucose ...reduction ...after AMI was associated with improved outcome". My reading was that in both actively treated arms of that study, while there was a statistically significant early reduction in blood glucose level (0.9mmol/L) compared with 'control', there was no benefit. Those with high sugars did badly, but active treatment didn't help. I think that you have to address, if only in a sentence, the NICE guideline on hyperglycaemia and ACS, given that the implication of

	your study would be that treatment of glucose should be beneficial.

REVIEWER	Harding, Scott Wellington Hospital, Department of Cardiology No competing interests
REVIEW RETURNED	11-Apr-2012

GENERAL COMMENTS	General comments This paper focuses on comparing the relative association of diabetes and admission blood glucose with mortality in NSTEMI and STEMI populations. They conclude that admission blood glucose is a strong predictor of mortality and that after adjustment for admission blood glucose and other factors, known diabetes is not associated with adverse outcome. The authors have previous published similar results for STEMI patients. Whilst this work represents and extension of their previous work it is not completely novel. Previous studies have demonstrated that hyperglycaemia on admission is a strong independent marker of adverse prognosis in acute coronary syndromes whether or not patients are diabetic and that hyperglycaemia may even be a stronger predictor than diagnosed diabetes. Specific comments 1. The authors provide no information about the categorization of diabetes by medical therapy (diet controlled, oral medication, insulin). This is a significant limitation and it would be interesting to know if outcomes varied by subgroup. 2. The authors provide no information regarding the number of patients who were given a diagnosis of diabetes during, or subsequent to, the index admission. Whilst this limitation is acknowledged it remains a deficiency of the paper. Previous studies have shown there is a high rate of undiagnosed diabetes in those presenting with MI. 3. It may be that admission blood glucose was a stronger predictor because the clinical categorization of impaired glucose metabolism was inadequate. 4. Is it just that “admission blood glucose” is a better measure of impaired glucose metabolism than an antecedent diagnosis of diabetes mellitus and that the 5. The methods state “The blood glucose used for the analysis was the first recorded at the time of the index admission, assayed in the hospital laboratory as part of routine investigations. Can the authors be more specific about when the blood samples were drawn? What proportion of the blood glucose measurements we drawn within the 1st 24 hours of admission. 6. If available BMI data should be included. 7. In the results section when discussing the influence of the admission glucose concentration on mortality in patients with or without diabetes the authors should report the actual HR and confidence intervals for mortality in the diabetic and non-diabetic groups rather than just report that they were statistically similar. 8. The authors make the following statement on page 12 of the

	discussion: “clinical studies support a possible causal link between hyperglycaemia and adverse prognosis after AMI, and also the benefit of active lowering of glucose in this setting.” And state on page: 13 “ However, if elevated glucose contributes directly to prognosis, active management is likely to confer greater benefit when delivered as early as possible, irrespective of subsequent diabetes status”. I think it is fair to say that the studies on the value of tight glycaemic control in MI have been inconclusive. DIGAMI-2 was negative and studies of tight glycaemic control in ICU units have also failed to show benefit with and excess of hypoglycaemic events. The discussion should be modified to reflect this.

REVIEWER	Henderson, Robert Nottingham University Hospitals NHS Trust, Cardiology I have no competing interests
REVIEW RETURNED	21-Apr-2012

GENERAL COMMENTS	This paper reports the influence of an antecedent diagnosis of diabetes mellitus and admission blood glucose level on 30 day and one year survival in 4,111 patients admitted to a coronary care unit with STEMI or NSTEMI. The main finding is that admission blood glucose was associated with 30 day and 1 year mortality, both in STEMI and NSTEMI patients. By contrast there was no association between a diagnosis of diabetes and outcome. Previous papers report that a diagnosis of diabetes mellitus and elevated blood glucose are both associated with an adverse outcome after acute myocardial infarction. The rationale for the analysis in this paper and what the results add to the literature should be more clearly described in the introduction and discussion sections. The study recruited over 4,000 patients over six years but a much higher number of acute coronary syndrome patients would have been expected from a catchment population of nearly one million. In the introduction the authors acknowledge that the majority of acute coronary syndromes in contemporary practice are NSTEMI, but in their data set 58.3% of the patients had STEMI. Can the authors comment? The authors state that the diagnosis of acute myocardial infarction was made according to the joint 2007 ECS-ACCF-AHA-WHF definition. The study commenced in 2002 and it is unclear whether the new definition of myocardial infarction was applied consistently over the entire duration of the study. Specifically did the biomarker used for the detection of myocardial necrosis or the criteria used for the diagnosis of myocardial infarction change over time? The authors state that the primary outcome measure was predefined, but it is unclear whether the outcome was defined when the registry was set up or when the authors planned their analysis. The primary outcome is defined as the “relative strength of association” but surely the primary outcome(s) is 30 day and all cause mortality.

	It is unsurprising that a diagnosis of diabetes is a less powerful predictor of mortality than blood glucose. It is well known that many patients with diabetes are undiagnosed, but blood glucose level is a continuous variable that is an indicator of infarct size and therefore likely to be related to outcome. The authors should consider this possibility in the discussion. Several other variables were associated with mortality but these are not considered in detail, either in the results or in the discussion. Were any of these variables more powerfully associated with mortality than blood glucose? How do these variables compare with variables associated with outcome in other large studies of ACS (e.g. GRACE)? Abstract The increase in HR per mmol/L for blood glucose is 0.07 (i.e. 7%) not 1.07 (107%) Page 6 The authors refer to “explanatory” variables but these variables simply show a statistical association with the primary outcome. Page 8 The authors refer to four time periods but only report three mortality rates (1st sentence). The authors also report that survival improved over the period of observation. This is a potentially interesting observation and more detail should be provided. It would also be of interest to see some information about the use of reperfusion therapy and revascularisation procedures over time. Page 8 &9 The subheadings for the univariate and multivariate analyses are confusing partly because post discharge mortality is considered under a separate subheading. Figure 1 It is unclear what the histograms in Figure 1 are showing. Is this number of patients?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Comments: In this observational study the authors' stated aim is to compare the relative strength of association (in STEMI and in nSTEMI) between outcome (death at 30 days and 1 year after index event) and two predictors - a prior diagnosis of diabetes mellitus and the 'admission' blood glucose concentration (more accurately, the first recorded laboratory-determined plasma glucose concentration) - when adjusted for other presumed or documented predictors.

Their finding is that while both prior diabetes and higher levels of admission blood glucose are associated with poorer outcomes after heart attack, the association is much stronger for the absolute level of glucose, and when blood glucose is included in the predictive model the association with diagnosed diabetes is lost. In their model, which includes blood glucose, diabetes was not an independent predictor of moratlity after heart attack. This is true for STEMI and nSTEMI - though interestingly the association between mortality and glucose appears to diminish over the year.
Abstract - Structured abstract. MINAP is Myocardial Ischaemia National Audit PROJECT rather than PROGRAMME.

Introduction - Good well-referenced introduction. Clearly-stated aim in last paragraph.

Response: Thank you for your comments. We have now corrected the error in the full form of the acronym MINAP in the manuscript.

Comments on Methods:

Comments: MINAP = project in para 1. Also suggest a more contemporary reference for the MINAP (Herrett E, Smeeth L, Walker L, Weston C. The Myocardial Ischaemia National Audit Project (MINAP) Heart 2010;96:1264-67) instead of the present ref 18.

Response: We have now used this reference at number 18 in place of the previous one.

Comments: Were all patients with prior diagnosis of diabetes type 2 diabetic?
Is it safe to assume that all 'admission' blood glucose measurements were performed on blood obtained within 12 hours of arrival at hospital, or before any treatment for hyperglycaemia was instigated?
You have some information on in-hospital treatment - do you have any on specific treatment to reduce raised blood glucose?

Response: In the MINAP dataset, information on the type of diabetes is not available. We are therefore unable to provide details of proportion of people with type 2 diabetes in our study. At our centre, it is routine practice to perform laboratory plasma glucose test along with other routine blood test, as soon as possible after admission with an acute myocardial infarction. Therefore in the vast majority of patients in our study, the recorded admission plasma glucose levels represent the levels within 12 hours of arrival at hospital. Furthermore patients with plasma glucose levels > 11.0 mmol/L at admission are treated with IV insulin therapy for first 24 hours as per the hospital policy. However information on in-patient glucose lowering therapies is incomplete in the MINAP dataset used for our study, and we were unable to consider it in the analysis.

Comments: In my comments regarding study design I have stated: I do not feel that my personal expertise in statistics is sufficient to critique the statistical techniques used (eg. fractional polynominals) - though the description of, and rationale for, the 'stats' is good.

Response: Thank you for your comments. The statistical analysis was undertaken as per the principles outlines in statistics literature and in liaison with a statistician with experience in conducting survival analysis.

Comments on Results

Comments: - the dates in line 1 are 2002 until 2009. I think that this should be 2002-2008 (as in other sections of the paper).

Response: We have now corrected this error in the manuscript on page 7.

Comments: You have chosen to express plasma glucose as mean with standard deviation. Was there a normal distribution of values? What about medians (with IQR)?

Response: The assumption of normality was checked and was reasonable for the distribution of plasma glucose. The medians (with IQR) for plasma glucose levels, for people with and without diabetes were 11.2 mmol/L (8.0 - 14.5) and 7.2 mmol/L (6.1 - 8.8) respectively.

Comments: I got confused at the start of the section on 'Mortality - univariate analysis. I was expecting 4 numbers - for those dying during hospitalisation, within 30 days, within 1 year and over the whole period available for study. Instead there were only three. What was the number of those dying in hospital after the index event? It's 319 isn't it (4111-3792)? There are then slight discrepancies between the numbers reported to have died after discharge and those having died after the index event (eg all deaths up to 30 days = 409; deaths after discharge up to 30 days = 106 - so deaths in hospital 303 not 319). I guess that this must reflect different cuts of the data.
How did you deal with missing data (particularly with missing glucose estimates)?

Response: We have now provided the mortality rate for in-patient deaths in the results section on page 8. We confirm that the total number of deaths as in-patient is in fact 319. The apparent discrepancy in the number of deaths as pointed out in the comments is due the fact that, 16 out of the total 319 patients who died as in-patient stayed as in-patients for more than 30 days. These 16 patients were therefore not included in the death count at 30 days. The remaining 303 patients (who died as in-patients but within 30 days) plus additional 106 patients who died after discharge but within 30 days account for the total 409 deaths at 30 days.

The proportions of people with missing values are provided for each variable in Table 1. For a total of 14.9% of patients the values for plasma glucose on admission were missing. The people with missing values were not excluded from the analysis but their values were set as missing.

Comments on Discussion

Comments: I would reword the first two sentences (eg "Both a prior diagnosis of diabetes and....This is the first study to compare the relative strengths of the association of .....)

Response: We have now reworded these two sentences in the manuscript on page which now reads:

It is well recognised that, both prior diagnosis of diabetes, and admission blood glucose concentration are associated with adverse outcome after AMI. In this report we compared the relative association of these two measures of dysglycaemia with survival after STEMI as well as NSTEMI.

Comments: You say that you show no trend to increased assoc between diabetes and mortality after AMI. But in your univariate analysis (table 2) the HR goes from 1.4 at 30 days to 1.58 at 1 yr to 1.65 at 912 days. Even in multivariate analysis the HR increases albeit the 95% CI straddles 1.0. Is there no trend here?

Response: We have already acknowledged the strong univariate association seen between diabetes and mortality under the section of Mortality - Univariate analysis on page 8. We felt that this association was nonsignificant and the trend less obvious on multivariate analysis. We have now revised the sentence in discussion on page 12 to reflect this. The sentence now reads:

While we observed such a trend on univariate analysis, this was attenuated in multivariate analysis, an observation which may relate to our inclusion of blood glucose as a covariate.

Comments: What if any effect would more aggressive treatment of raised blood glucose in those with prior diabetes have on your findings regarding the relative strengths of associations - there is evidence (kosiborod, MINAP annual report - you mention this in Discussion) that for any given level of admission blood glucose a person with diabetes is more likely to be given insulin.

Response: We appreciate reviewer's thoughts on this important point. There is a possibility that the aggressive management of elevated glucose levels selectively in patients with known diabetes would have improved their survival compared to those with elevated glucose but without known diabetes . This may in turn contribute to the finding in our analysis that diabetes status is not a significant predictor of mortality. However if this true, it further strengthen our conclusion that diabetes is not a independent predictor of mortality when glucose is considered concomitantly; and that if elevated glucose contribute to the prognosis, active management as early as possible irrespective of diabetes status is likely to be beneficial. Due to the lack of complete data on in-patient glucose lowering treatment, we are unable to consider information on glucose lowering treatment in our analysis.

Comments: I think you are pushing it a little to use DIGAMI 2 (ref17) to support your statement that "active management of blood glucose ...reduction ...after AMI was associated with improved outcome". My reading was that in both actively treated arms of that study, while there was a statistically significant early reduction in blood glucose level (0.9mmol/L) compared with 'control', there was no benefit. Those with high sugars did badly, but active treatment didn't help.

Response: We recognise that in DIGAMI 2 there was no overall survival benefit from active management of hyperglycaemia. However in that trial, *effective* lowering of blood glucose to target levels *was* associated with benefit. The findings of the DIGAMI 2 trail and its implication on practice continues to be debated, not the least because the study was underpowered, the pre-specified glucose levels were not achieved in the intervention arms and there was no difference in the achieved glucose levels in the interventions and the control arms. (Anantharaman A, Heatley M, Weston C. Hyperglycaemia in acute coronary syndromes: risk-marker or therapeutic target. Heart 2009;95:697–703).The glucose difference achieved between the groups was only 0.9 mmol/l, and the target fasting blood glucose was not reached consistently (9.1 mmol/l in the treatment group).We have now revised our statement on page 12 related to the DIGAMI trials in the discussion. Please refer to response to the next comment for more details.

Comments: I think that you have to address, if only in a sentence, the NICE guideline on hyperglycaemia and ACS, given that the implication of your study would be that treatment of glucose should be beneficial.

Response: Thank you for your suggestion. We have now revised the last part of the second paragraph on page 12 in the original manuscript. Furthermore we have added a new paragraph on page 12 providing information on the NICE guidelines on hyperglycaemia (new reference added at number 27) as well as on a position statement from the American Heart Association (new reference added at number 28) in this area.

The information in the new paragraph on page 12 now reads.

While observational studies show consistently the adverse association between hyperglycaemia and outcomes post AMI, results of the RCTs of active management of blood glucose have been inconsistent.(16,17) However, in such trials, effective reduction in blood glucose with an intervention after AMI was associated with improved prognosis.(16) The guidelines from professional societies in this area differ in their recommendations.(27,28) In the North American guidelines, intensive glucose control is recommended in patients with AMI and significant hyperglycaemia (blood glucose levels > 10.0 mmol/L) admitted in an intensive care unit.(28) In contrast, the National Institute for Health and Clinical Excellence guidance recommends against routine use of intensive insulin therapy to manage hyperglycaemia (blood glucose levels > 11.0 mmol/L) in patients with acute coronary syndrome.(27) The latter guidelines highlighted a need for randomised controlled trials addressing specific gaps in knowledge this area.

Comments by Reviewer: 2

General comments:

This paper focuses on comparing the relative association of diabetes and admission blood glucose with mortality in NSTEMI and STEMI populations. They conclude that admission blood glucose is a strong predictor of mortality and that after adjustment for admission blood glucose and other factors, known diabetes is not associated with adverse outcome. The authors have previous published similar results for STEMI patients. Whilst this work represents and extension of their previous work it is not completely novel. Previous studies have demonstrated that hyperglycaemia on admission is a strong independent marker of adverse prognosis in acute coronary syndromes whether or not patients are diabetic and that hyperglycaemia may even be a stronger predictor than diagnosed diabetes.

Response: While studies published previously in this area mainly reported *individual* relationships between mortality and either diabetes diagnosis or blood glucose concentration, we studied the *relative* association of admission hyperglycaemia and antecedent diabetes in patients admitted with *both NSTEMI and STEMI*, in a contemporary UK population. The majority of patients admitted with

AMI in contemporary practice have NSTEMI. Furthermore two thirds of patients with admission hyperglycaemia but without known diabetes are not actively treated with glucose lowering agents. Findings of our study have implication on practice as we demonstrates that admission hyperglycaemia following AMI are associated with adverse outcomes, irrespective of presentation of AMI (NSTEMNI vs STEMI) or underlying diabetes status.

Specific comments

Comment 1. The authors provide no information about the categorization of diabetes by medical therapy (diet controlled, oral medication, insulin). This is a significant limitation and it would be interesting to know if outcomes varied by subgroup.

Response: We appreciate reviewer's suggestions. However the information on medical therapies for diabetes was incomplete in the dataset. Furthermore the study does not have enough power to come to any meaning conclusion on relationship between medical therapies and outcomes in subgroup of patients with diabetes.

Comment 2. The authors provide no information regarding the number of patients who were given a diagnosis of diabetes during, or subsequent to, the index admission. Whilst this limitation is acknowledged it remains a deficiency of the paper. Previous studies have shown there is a high rate of undiagnosed diabetes in those presenting with MI. It may be that admission blood glucose was a stronger predictor because the clinical categorization of impaired glucose metabolism was inadequate.

Response: We appreciate reviewer's comments on this limitation of the study. However, the gold standard test of oral glucose tolerance test (OGTT) required for diagnosing previously undetected glucose abnormalities was not conducted on patients in our study. We therefore do not have definite information on previously undiagnosed diabetes or impaired glucose tolerance in our study.

Comment 4. Is it just that "admission blood glucose" is a better measure of impaired glucose metabolism than an antecedent diagnosis of diabetes mellitus and that the

The methods state "The blood glucose used for the analysis was the first recorded at the time of the index admission, assayed in the hospital laboratory as part of routine investigations. Can the authors be more specific about when the blood samples were drawn? What proportion of the blood glucose measurements we drawn within the 1st 24 hours of admission.

Response: At our centre, laboratory plasma glucose test are performed along with other routine blood test, as soon as possible on arrival in patients with an acute myocardial infarction. Therefore, it is very likely that in majority of patients in our study the recorded admission plasma glucose levels represent the levels within 12 to 24 hours of admission. However, precise information on time of collection of blood glucose sample in relation to time of arrival is not recorded in the MINAP dataset. We are therefore unable be provide information on proportion of people in whom blood glucose levels were drawn within first 24 hours.

Comment 6. If available BMI data should be included.

Response: Regrettably the data on Body Mass Index (BMI) was not available on significant proportion of patients and therefore was not included in the paper.

Comment 7. In the results section when discussing the influence of the admission glucose concentration on mortality in patients with or without diabetes the authors should report the actual HR and confidence intervals for mortality in the diabetic and non-diabetic groups rather than just report that they were statistically similar.

Response: The associated of blood glucose with mortality in patients with and without diabetes was assessed as such by conducting a separate multivariate analysis, including a term for interaction between diabetes diagnosis and admission glucose concentration. The hazard ratios for the interaction term are provided in the results section under the subsection of 'Admission glucose concentration – influence on mortality in patients with or without diabetes' The hazard ratios were not

statistically significantly different, suggesting that there is no difference in association of relationship between admission glucose and mortality in patients with and without diabetes.

Comment 8. The authors make the following statement on page 12 of the discussion: “clinical studies support a possible causal link between hyperglycaemia and adverse prognosis after AMI, and also the benefit of active lowering of glucose in this setting.” And state on page: 13 “ However, if elevated glucose contributes directly to prognosis, active management is likely to confer greater benefit when delivered as early as possible, irrespective of subsequent diabetes status”. I think it is fair to say that the studies on the value of tight glycaemic control in MI have been inconclusive. DIGAMI-2 was negative and studies of tight glycaemic control in ICU units have also failed to show benefit with and excess of hypoglycaemic events. The discussion should be modified to reflect this.

Response: We understand reviewers comments in this area. Since the observational data from a number of studies have shown a strong and independent association between admission glucose levels and outcomes, the inconsistencies in results of DIGAMI and other studies remains widely debated. To date, the only RCT of active management of hyperglycaemia in the context of AMI to have achieved a significant difference in final blood glucose levels between intervention and control groups was DIGAMI, and this is the one study to show benefit from intervention.
DIGAMI -2 failed to achieve the target glucose levels in intervention arm and there was only a small separation of glucose levels in the intervention and control arms. Furthermore, the study was hampered by significant crossover of patients from usual care to active glucose management. This is reflected in guidelines by various professions societies which differ in their recommendations. We have now added more information on this in a new paragraph under the discussion section in the manuscript. Please refer to our response to the last comment made by Reviewer 1.
Comments by Reviewer: 3

Comments: This paper reports the influence of an antecedent diagnosis of diabetes mellitus and admission blood glucose level on 30 day and one year survival in 4,111 patients admitted to a coronary care unit with STEMI or NSTEMI. The main finding is that admission blood glucose was associated with 30 day and 1 year mortality, both in STEMI and NSTEMI patients. By contrast there was no association between a diagnosis of diabetes and outcome.

Previous papers report that a diagnosis of diabetes mellitus and elevated blood glucose are both associated with an adverse outcome after acute myocardial infarction. The rationale for the analysis in this paper and what the results add to the literature should be more clearly described in the introduction and discussion sections.

Response: We feel that we have already described this in the relevant sections of the manuscript. Please see our response to the ‘General comments’ by reviewer 2.

Comments: The study recruited over 4,000 patients over six years but a much higher number of acute coronary syndrome patients would have been expected from a catchment population of nearly one million. In the introduction the authors acknowledge that the majority of acute coronary syndromes in contemporary practice are NSTEMI, but in their data set 58.3% of the patients had STEMI. Can the authors comment?

Response: The apparent, relatively small proportion of people with NSTEMI in our study is likely to be due to two main factors. The study cohort represents people admitted directly to the Leicester Hospitals as well as those referred to our tertiary centre from peripheral hospitals. As the referred patients are usually complicated patients with STEMI, it would have accounted for relatively high proportion of patients with STEMI in our cohort. Secondly, in the early years of the MINAP project, data on only STEMI were collected. Currently, data collected for MINAP are gathered mainly in the setting of the coronary care unit, likely leading to an ongoing selection bias.

Comments: The authors state that the diagnosis of acute myocardial infarction was made according to the joint 2007 ECS-ACCF-AHA-WHF definition. The study commenced in 2002 and it is unclear whether the new definition of myocardial infarction was applied consistently over the entire duration of the study. Specifically did the biomarker used for the detection of myocardial necrosis or the criteria used for the diagnosis of myocardial infarction change over time?

Response: The criteria applied for the definition of AMI remained consistent throughout the period of this study. Troponin measurement was available and used throughout. As already noted, STEMI events were preferentially captured in the early period of MINAP, with increasing proportions of NSTEMI events over the course of the study period.

Comments: The authors state that the primary outcome measure was predefined, but it is unclear whether the outcome was defined when the registry was set up or when the authors planned their analysis. The primary outcome is defined as the "relative strength of association" but surely the primary outcome(s) is 30 day and all cause mortality.

Response: The primary outcome was defined at the beginning of this retrospective study. We agree that the primary outcome should be stated as suggested in the comment. We have now revised this statement in the manuscript on page 6.

Comments: It is unsurprising that a diagnosis of diabetes is a less powerful predictor of mortality than blood glucose. It is well known that many patients with diabetes are undiagnosed, but blood glucose level is a continuous variable that is an indicator of infarct size and therefore likely to be related to outcome. The authors should consider this possibility in the discussion.

Response: We agree that blood glucose may indicate previously unrecognised diabetes, and we have acknowledged this in the manuscript (page 11). However elevated admission blood glucose is not a reliable indicator of the diagnosis of diabetes, as we have also noted in the discussion on page 11.

Comments: Several other variables were associated with mortality but these are not considered in detail, either in the results or in the discussion. Were any of these variables more powerfully associated with mortality than blood glucose? How do these variables compare with variables associated with outcome in other large studies of ACS (e.g. GRACE)?

Response: The details of variables considered in the multivariate analysis and the quantitative estimates of association between variables and mortality at various time points are given in table 3 and table 3A and discussed under the subsections of Mortality – Multivariate analysis. As the focus of this paper was to highlight relative association between the two measures of dysglycaemia, we avoided any in depth discussion on other significant predictors of mortality, all of which were as expected.

Comments on Abstract: The increase in HR per mmol/L for blood glucose is 0.07 (i.e. 7%) not 1.07 (107%)

Response: While we have interpreted the meaning of HR correctly, for the sake of presentation the information on the HR was provided in that manner in the abstract. We have made a correction to the statement in order to present full information on various Hazard ratio and confidence intervals. The sentence in the results section of the abstract now reads:

In contrast, after adjusting for covariates, admission glucose showed robust and independent association with mortality in the entire cohort (HR: 30 days 1.07 (1.04 – 1.10); 1-year 1.05 (1.03 – 1.08)), and in the subgroup of STEMI (30-days 1.07 (1.03 – 1.10); 1-year1.07 (1.04 – 1.10)), and NSTEMI (HR 30 days 1.07 (1.00 - 1.14); 1-year 1.02 (0.97 - 1.06)).

Comments:
Page 6 - The authors refer to "explanatory" variables but these variables simply show a statistical association with the primary outcome.

Response: These variables do show association with outcome. However, there can be little doubt that many of these variables contribute to adverse outcome, and in this context are "explanatory". We have altered the sentence to read "clinical variables"

Comments:

Page 8_The authors refer to four time periods but only report three mortality rates (1st sentence). The authors also report that survival improved over the period of observation. This is a potentially interesting observation and more detail should be provided. It would also be of interest to see some information about the use of reperfusion therapy and revascularisation procedures over time.

Response: Deaths during hospitalisation have now been reported on page 8. We recognise the interest in improving survival over time, and that the use of coronary revascularisation may have increased. However these were not the main focus of this analysis of the relationship between measures of dysglycaemia and survival, and we do not feel that extensive discussion of these matters is relevant to this analysis.

Comments:

Page 8 &9
The subheadings for the univariate and multivariate analyses are confusing partly because post discharge mortality is considered under a separate subheading.

Response: We do not consider our presentation of the data to be confusing. We have presented data separately on post-discharge mortality to emphasise the ongoing association between glucose and adverse outcome long after the index admission, a very important clinically relevant observation.

Comments:

Figure 1
It is unclear what the histograms in Figure 1 are showing. Is this number of patients?

Response: The Figure legend indicates the meaning of the figure. The 'X' axis represents glucose levels, and the bars the number of people at various glucose levels. The Solid and dotted lines represents the odds ratios and confidence intervals respectively. We have now revised the Figure legends to provide more clear information.