Prognostic impact of admission blood glucose for all-cause mortality in patients with acute coronary syndromes: added value on top of GRACE risk score

Ana T Timóteo, Ana L Papoila, Pedro Rio, Fernando Miranda, Maria L Ferreira and Rui C Ferreira

European Heart Journal: Acute Cardiovascular Care published online 31 March 2014
DOI: 10.1177/2048872614528858

The online version of this article can be found at:
http://acc.sagepub.com/content/early/2014/03/31/2048872614528858

Published by:
European Society of Cardiology

ESC Working Group on Acute Cardiac Care

and

http://www.sagepublications.com

Additional services and information for European Heart Journal: Acute Cardiovascular Care can be found at:

Email Alerts: http://acc.sagepub.com/cgi/alerts
Subscriptions: http://acc.sagepub.com/subscriptions
Reprints: http://www.sagepub.com/journalsReprints.nav
Permissions: http://www.sagepub.com/journalsPermissions.nav

>> OnlineFirst Version of Record - Mar 31, 2014

What is This?
Prognostic impact of admission blood glucose for all-cause mortality in patients with acute coronary syndromes: added value on top of GRACE risk score

Ana T Timóteo1, Ana L Papoila2,3, Pedro Rio1, Fernando Miranda4, Maria L Ferreira1 and Rui C Ferreira1

Abstract

Background: Abnormal glucose metabolism is a predictor of worse outcome after acute coronary syndrome (ACS). However, this parameter is not included in risk prediction scores, including GRACE risk score. We sought to evaluate whether the inclusion of blood glucose at admission in a model with GRACE risk score improves risk stratification.

Methods: Study of consecutive patients included in a single centre registry of ACS. Our primary endpoint was the occurrence of all-cause mortality at one-year follow-up. The ability of the two logistic regression models (GRACE risk score alone and in combination with blood glucose) to predict death was analysed. Continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI), with corresponding 95% confidence intervals (CIs), were also calculated.

Results: We included 2099 patients, with a mean age of 64 (SD=13) years, 69% males. In our sample, 55.1% presented with ST-segment elevation ACS and 13.1% in Killip class ≥2. Only 25% were known diabetic at admission. In-hospital mortality was 5.8% and 9.7% at one-year follow-up. The best cut-point for blood glucose was 160 mg/dl (sensitivity 62% and specificity 68%), and 35.2% of the patients had increased levels. This group was elderly, had more prevalence of cardiovascular risk factors, worse renal function and GRACE score as well as more frequently Killip class ≥2. Treatment was similar in both groups besides less frequent use of clopidogrel in high glycaemic patients. The hyperglycaemia group had higher one-year mortality (17.2% vs. 5.6%, p<0.001). Moreover, binary blood glucose remained a predictor of death independently of the GRACE risk score and the presence of diabetes (odds ratio (OR) 1.99, 95% CI 1.40–2.84, p<0.001). The inclusion of blood glucose, as a continuous variable, in a logistic regression model with GRACE score, increased the area under the ROC curve from 0.80 to 0.82 (p=0.018) as well as the goodness-of-fit and was associated with an improvement in both the NRI (37%) and the IDI (0.021), suggesting effective reclassification.

Conclusions: A blood glucose level on admission ≥ 160 mg/dl is an independent predictor of mortality in medium-term follow-up. It offers an incremental predictive value when added to the GRACE risk score, although with a modest magnitude of improvement, probably due to the high predictive performance of the GRACE risk score alone.

Keywords
Admission blood glucose, GRACE risk score, acute coronary syndromes, prognosis

Received: 18 November 2013; accepted: 3 March 2014

1Cardiology Department, Santa Marta Hospital, Centro Hospitalar de Lisboa Central, Lisbon, Portugal
2Biostatistics Department, CEAUL, Medical Sciences Faculty, New University of Lisbon, Portugal
3Research Department, Hospital Dona Estefânia, Centro Hospitalar de Lisboa Central, Lisbon, Portugal
4Clinical Pathology Department, Santa Marta Hospital, Centro Hospitalar de Lisboa Central, Lisbon, Portugal

Corresponding author:
Ana Teresa Timóteo, Cardiology Department, Hospital Santa Marta, Rua Santa Marta, 1169-024 Lisboa, Portugal.
E-mail: ana_timoteo@yahoo.com
Introduction

Elevated admission blood glucose is an important marker of worse outcome in patients with myocardial infarction.1 It is useful in patients both with and without diabetes.2,9 It is usually caused by stress hyperglycaemia induced by catecholamines, which, in turn, are correlated with myocardial lesion extension.1 However, risk scores applied in clinical practice do not include this variable.

The Global Registry of Acute Coronary Events (GRACE) risk score is a validated and established score for risk stratification of patients with acute coronary syndromes, obtained from a multicentre registry.10 It is used worldwide with very good predictive value for short- and medium-term all-cause mortality. It incorporates several clinical and laboratory variables to which a score is given to obtain the final score. Although better than previous risk scores, some patients are still incorrectly classified and some improvement in predictive accuracy would be important, particularly with the use of an easily obtainable variable.

Few studies are found in the literature that assessed the incremental prognostic value of admission blood glucose in combination with the GRACE risk score. However, these studies are somewhat small and showed no significant benefit.11,12 We sought to investigate the incremental value of admission blood glucose when considered with the GRACE risk score for the prediction of all-cause mortality at one-year, in a large sample of patients with the whole spectrum of acute coronary syndromes.

Methods

This is an observational study of all consecutive patients admitted to our intensive care unit (ICU) with ACS (with and without ST-segment elevation) during the years 2008 to 2010. Data were collected prospectively and recorded on a computer database of ACS patients admitted to our institution’s ICU (single-centre registry of ACS). Inclusion criteria were a history of chest pain at rest or other symptoms suggestive of an ACS, with the most recent episode occurring within 24 hours of admission. This could be associated with new or presumed new significant ST-segment–T wave changes/new left bundle branch block or elevated levels of biomarkers of myocardial damage (cardiac troponin I and creatine kinase). Myocardial infarction was defined by a rise and/or fall of cardiac troponin I with at least one value above 0.06 ng/ml. We evaluated demographic characteristics of the patients, risk factors for coronary artery disease, previous cardiac history, laboratorial data and vital signs on admission as well as in-hospital treatment. Automated laboratory equipment (Beckman Coulter LXiTM analyser) was used for glucose determination by the glucose-oxidase method (coefficient of variation: 2.0%).

We enrolled all consecutive patients if they had a record of admission blood glucose. There were no exclusion criteria.

Patients with increased blood glucose on admission were defined by a cut-off obtained with the statistical analysis described below.

Hypertension, diabetes and hyperlipidaemia were defined as either previously known or on specific therapy. Patients that had smoked during the previous six months were classified as smokers and were self-reported. Estimated glomerular filtration rate (eGFR) was calculated according to the Cockcroft–Gault formula.13 For each patient, a numerical scoring according to the previously described GRACE risk score was calculated from the initial clinical history, electrocardiogram and laboratory values collected on admission.10

Follow-up was obtained for every patient that survived to discharge by reviewing the medical records and/or by telephone interview with the patient or family members at 30 days and one year after admission. Follow-up information was obtained in 99.8% of the patients. The study primary endpoint was all-cause mortality at one-year follow-up.

The study complies with the Declaration of Helsinki and informed consent was obtained from all the subjects.

Statistical analysis

Continuous variables are expressed as mean (SD) and groups were compared with Student’s t-test. Categorical variables are expressed as percentage and Pearson’s chi-squared test or Fisher’s exact test were used, whenever appropriate.

Two logistic regression models were fitted to the data, one with the GRACE risk score alone and the other with the inclusion of blood glucose as a continuous variable. Predictive and discriminative abilities of these models were assessed by the Hosmer–Lemeshow goodness of fit test and by the area under the receiver operating characteristic (ROC) curve (AUC), respectively. The former compares the observed frequencies of patients with the event of interest with the expected frequencies based on the values of the estimated probabilities obtained by the logistic regression models. In this test, a high p-value (non-significant) indicates that the model is performing well and has a good fit. The AUC ranges from 0 to 1 and provides a measure of the model’s ability to discriminate between those subjects who experience the outcome of interest and those who do not. An AUC equal to 0.5 means no classification accuracy. To compare the AUCs from each of these models, the method described by DeLong et al. was used.14

Continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were also calculated. The net proportion of patients who died (with events) with higher probabilities of death (NRIevent) and of patients who did not die (without events) with lower probabilities of death (NRInon-event) were calculated considering both models. The NRI is the sum of NRIevent and NRInon-event and quantifies the correctness of upward and
downward reclassification or movement of predicted probabilities as a result of adding a new marker.13 The IDI is a measure of the improvement in prediction and may be viewed as the difference between improvement in average sensitivity and average 1-specificity.16

Regarding the categorization of blood glucose, minimum p-value approach was used. This method obtains the best cut-point from a grid of marker values that is associated with the minimum chi-squared p-value.17 A new logistic regression model was fitted considering the GRACE risk score and the categorized blood glucose, as independent variables.

For all comparisons, a p-value ≤ 0.05 was considered statistically significant. Whenever appropriate, 95% confidence intervals (CIs) were calculated.

Statistical analysis was carried out using IBM SPSS Statistics, Version 19.0 (IBM Corp., North Castle, NY, USA) and R software.18

Results

From a total of 2216 consecutive patients included in our registry, 2099 had information about admission blood glucose and were included in the study, with a mean age of 64 (SD=13) years, 69% males. The population baseline characteristics are described in Table 1. The in-hospital, 30-day and one-year mortality rates were 5.1%, 5.8% and 7.8% respectively.

By ROC curve analysis, the AUC of blood glucose for the prediction of one-year mortality was 0.68 (95% CI 0.64–0.72). Univariable analysis showed that blood glucose at admission, as a continuous variable, is a predictor of outcome (OR 1.07, 95% CI 1.05–1.08, p < 0.001, per 10 mg/dl increase) and it remained an independent predictor of mortality after adjustment for the GRACE risk score and for the presence of diabetes (OR 1.04, 95% CI 1.02–1.06, p < 0.001).

Models with GRACE risk score alone and after inclusion of blood glucose were then fitted to the data. The AUC increased significantly after the inclusion of blood glucose in the model (AUC=0.80 vs. AUC=0.82; p=0.018) (Figure 1) as did the goodness of fit (Table 2). Overall, the inclusion of blood glucose in a model with GRACE risk score was associated with a NRI of 37%, suggesting effective reclassification. Significant reclassification occurred mainly in the non-events group. In fact, for NRI non-events, a net 48% of patients who did not die had a substantial and significant reduction of the calculated risk. The IDI again showed that the model performance was improved by adding blood glucose to the GRACE risk score (IDI = 0.021) and, although modest, it was statistically significant.

Aware of the importance of biomarker cut-points in daily clinical practice, minimum p-value approach was used in order to find the blood glucose level that best discriminates the occurrence of all-cause mortality at one-year follow-up. A value of 160 mg/dl was obtained (Figure 2), with a sensitivity of 62% and a specificity of 68%. Patients with increased blood glucose were older, less often males, and had more risk factors for coronary artery disease, as well as previous stroke/transient ischemic attack (Table 1). They presented more often as a STEMI and with signs of heart failure. Renal insufficiency was more prevalent. They were more often submitted to coronary angiography and had more multivessel disease. Treatment was similar, except for clopidogrel, which was less frequently prescribed in patients with increased admission glucose. Mortality was significantly higher in this group (p<0.001).

Finally, the results of a new logistic regression model showed that blood glucose, as a binary variable, remained a predictor of death independently of the GRACE risk score and the presence of diabetes (OR 1.99, 95% CI 1.40–2.84, p<0.001).

Discussion

Elevated blood glucose level at admission for myocardial infarction is associated with worse outcome in both non-diabetic and diabetic patients.1–9 In fact, in a broad ACS population, hyperglycaemia at admission is a short-term and long-term prognostic marker. A high glucose level at admission is often attributed to ‘stress hyperglycaemia’ and might reflect an acute response to the hyperadrenergic state, with catecholamine release and induction of glycoenolysis.1 It is also associated with the increase in free fatty acids, insulin resistance, inactivation of nitric oxide and the production of oxygen reactive species, generating oxidative stress, as well as enhanced thrombin formation, platelet activation and fibrin clot resistance to lysis.19 Hyperglycaemia is associated with impaired coronary flow before reperfusion therapy in ST-elevation myocardial infarction patients.20

A report from the GRACE registry showed that short-term and six-month mortality was increased significantly with higher admission glucose levels in patients across the whole spectrum of acute coronary syndromes. This association is probably mainly driven by an increased risk of early death, consistent with the paradigm that admission glucose level is a marker of stress rather than a reflection of a general glucometabolic state.21 A U-shaped curve of risk associated with admission glucose level is described, consistent with previous reports of adverse outcome associated with low levels (< 100 mg/dl) in patients presenting with an acute myocardial infarction and in diabetic patients with ACS.1 It might be related to inadequate stress response. This registry also showed the association between fasting glucose levels and short-term and six-month mortality, suggesting that this might be a better independent marker than admission glucose level.1
Two previously published papers showed no benefit in risk stratification after ACS with the inclusion of admission blood glucose in a logistic regression model with GRACE risk score. However, the samples were relatively small and in one case only hospital mortality was analysed.\textsuperscript{11,12}

Correia et al. studied a small sample (148 patients) with only non-ST segment elevation ACS.\textsuperscript{11} There was no benefit in either AUC or NRI. Admission blood glucose was introduced directly inside the GRACE risk score model without any type of validation. De Mulder et al. studied a larger sample (550 patients), but the inclusion period was from 2003 to 2006, and does not reflect contemporary treatment.\textsuperscript{12} Both AUC and NRI improvement showed a trend, although not of statistical significance. The data from our large and unselected population confirmed that admission glucose is an independent predictor of all-cause mortality in the whole spectrum of acute coronary syndromes, even after adjustment for diabetic status and GRACE risk score. They also showed significant benefit in risk stratification after the inclusion in a model with the GRACE risk score.

<table>
<thead>
<tr>
<th>Clinical characteristics of both groups according to glucose levels.</th>
<th>Total n=2099</th>
<th>Glucose &lt; 160 mg/dl n=1361</th>
<th>Glucose ≥ 160 mg/dl n=738</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64 ± 13</td>
<td>63 ± 13</td>
<td>66 ± 14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>69.1</td>
<td>71.1</td>
<td>65.3</td>
<td>0.007</td>
</tr>
<tr>
<td>Risk factors (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>65.7</td>
<td>63.0</td>
<td>70.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>49.8</td>
<td>51.5</td>
<td>46.6</td>
<td>0.036</td>
</tr>
<tr>
<td>Diabetes</td>
<td>25.5</td>
<td>10.9</td>
<td>52.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>36.4</td>
<td>40.4</td>
<td>29.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous history (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>15.7</td>
<td>15.5</td>
<td>16.1</td>
<td>0.756</td>
</tr>
<tr>
<td>PCI</td>
<td>10.5</td>
<td>11.5</td>
<td>8.7</td>
<td>0.055</td>
</tr>
<tr>
<td>CABG</td>
<td>4.2</td>
<td>3.7</td>
<td>5.1</td>
<td>0.159</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>6.3</td>
<td>5.1</td>
<td>8.5</td>
<td>0.002</td>
</tr>
<tr>
<td>Initial presentation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STEMI (%)</td>
<td>55.1</td>
<td>52.5</td>
<td>59.8</td>
<td>0.002</td>
</tr>
<tr>
<td>Killip class &gt;1 (%)</td>
<td>13.1</td>
<td>8.4</td>
<td>21.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>78 ± 19</td>
<td>76 ± 18</td>
<td>81 ± 21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>133 ± 28</td>
<td>134 ± 28</td>
<td>132 ± 29</td>
<td>0.121</td>
</tr>
<tr>
<td>Laboratory data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR &lt; 60 ml/min per 1.73 m(^2) (%)</td>
<td>28.1</td>
<td>24.2</td>
<td>35.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood glucose (mg/dl)</td>
<td>163 ± 82</td>
<td>119 ± 21</td>
<td>244 ± 90</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GRACE risk score</td>
<td>145 ± 36</td>
<td>138 ± 34</td>
<td>158 ± 36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF &lt; 35% (%)</td>
<td>7.5</td>
<td>5.2</td>
<td>11.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary angiography (%)</td>
<td>76.9</td>
<td>75.5</td>
<td>79.5</td>
<td>0.032</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>66.8</td>
<td>63.1</td>
<td>72.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Treatment (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA</td>
<td>97.4</td>
<td>97.7</td>
<td>96.7</td>
<td>0.234</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>93.3</td>
<td>94.1</td>
<td>91.7</td>
<td>0.046</td>
</tr>
<tr>
<td>ACEI</td>
<td>86.7</td>
<td>86.3</td>
<td>87.3</td>
<td>0.596</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>81.8</td>
<td>82.4</td>
<td>80.9</td>
<td>0.438</td>
</tr>
<tr>
<td>Statin</td>
<td>92.6</td>
<td>93.3</td>
<td>91.2</td>
<td>0.093</td>
</tr>
<tr>
<td>PCI</td>
<td>74.6</td>
<td>74.2</td>
<td>75.3</td>
<td>0.607</td>
</tr>
<tr>
<td>CABG</td>
<td>1.1</td>
<td>1.0</td>
<td>1.4</td>
<td>0.535</td>
</tr>
<tr>
<td>All-cause mortality (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>5.1</td>
<td>2.8</td>
<td>11.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>One-year mortality</td>
<td>7.8</td>
<td>5.6</td>
<td>17.2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; TIA: transient ischemic attack; STEMI: ST elevation myocardial infarction; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; ASA: acetylsalicylic acid; ACEI: angiotensin converting enzyme inhibitor.

Two previously published papers showed no benefit in risk stratification after ACS with the inclusion of admission blood glucose in a logistic regression model with GRACE risk score. However, the samples were relatively small and in one case only hospital mortality was analysed.\textsuperscript{11,12}

Correia et al. studied a small sample (148 patients) with only non-ST segment elevation ACS.\textsuperscript{11} There was no benefit in either AUC or NRI. Admission blood glucose was introduced directly inside the GRACE risk score model without any type of validation. De Mulder et al. studied a larger sample (550 patients), but the inclusion period was from 2003 to 2006, and does not reflect contemporary treatment.\textsuperscript{12} Both AUC and NRI improvement showed a trend, although not of statistical significance. The data from our large and unselected population confirmed that admission glucose is an independent predictor of all-cause mortality in the whole spectrum of acute coronary syndromes, even after adjustment for diabetic status and GRACE risk score. They also showed significant benefit in risk stratification after the inclusion in a model with the GRACE risk score.

Mere associations with incident all-cause mortality, although important, do not automatically mean that adding a new marker to traditional risk prediction models will improve outcome risk prediction. Therefore, we performed...
tests to discriminate and calibrate different prediction models. Discriminative analysis of a model with GRACE risk score alone and after admission glucose inclusion showed that the AUC increased significantly. The predictive performance also improved. Considering the other new statistical metrics, recently proposed, to quantify the degree of correct reclassification, the inclusion of glucose in a model with GRACE risk score was associated with a NRI of 37%, suggesting effective reclassification. The new model better identifies the group without events. The IDI again showed that the model performance was significantly, although slightly, improved by adding glycaemia to the GRACE risk score.

The magnitude of improvement was small. However, in the presence of a fairly robust risk score, such as in the case of the GRACE risk score, the quantitative improvement in model performance introduced by adding new variables to the existing model is expected to be small. Also the new model better identifies those who do not have events than those who do. The new model significantly reduced the calculated risk in 48% of those without events. Thus the new model (with the addition of admission blood glucose to the GRACE score) is better at identifying ‘truly low-risk’ patients and is as good as in identifying patients who develop events. This might not be ideal when we are evaluating a risk score to identify high-risk patients. However, recent cardiovascular disease guidelines are encouraging a practice shift toward greater focus on identification of ‘truly low-risk’ patients instead of focusing on identification of high-risk patients. This allows a better selection of patients avoiding unnecessary interventions that might increase costs as well as the risk of procedure-related adverse events.

Limitations
This is a single-centre study, which might limit its conclusions. It is also a retrospective study. It might not be applicable to other populations with different baseline characteristics. In particular, our population has a predominance of ST elevation myocardial infarction patients, explained by the fact that we are a tertiary centre which receives many patients from other hospitals for primary percutaneous coronary intervention. However, this does not reflect the
distribution in other cohort studies of ACS and some caution should be used when translating our results for other cohorts.

The cut-off proposed by the present work was not externally validated. However, other authors from Spain and Italy (Mediterranean countries) proposed similar cut-offs (140 mg/dl and 170 mg/dl, respectively).23–25 Other, Eastern European, countries suggest higher cut-points (≥ 200 mg/dl).26,27 Probably there is some genetic/environmental explanation for these results and local studies seem to be important.

Conclusions
In a population of patients with the whole spectrum of acute coronary syndromes, blood glucose adds prognostic information to established risk factors, even in combination with the GRACE risk score. A level at admission ≥ 160 mg/dl is an independent predictor of mortality in medium-term follow-up. We encourage its wider use.

Conflict of interest
The authors declare that there is no conflict of interest.

Funding
The statistical analysis performed by ALP was supported by the Fundação Nacional para a Ciência e Tecnologia, Portugal – FCT, under the project PEst-OE/MAT/UI0006/2014.

References

