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Plasma glucose and not haemoglobin or renal function predicts mortality in patients with STEMI complicated with cardiogenic shock

ABSTRACT

OBJECTIVE AND BACKGROUND
To assess the predictive value of three biomarkers for mortality in ST-segment elevation myocardial infarction (STEMI) with cardiogenic shock
STEMI complicated by cardiogenic shock accounts for the majority of STEMI related deaths. Patients with STEMI and hyperglycemia, anemia or kidney dysfunction on admission have a poor prognosis. As data on the combination of those three established predictors of mortality are sparse in STEMI with cardiogenic shock, the objective of the current study was to investigate their predictive value in STEMI patients with cardiogenic shock.

METHODS AND RESULTS
Between 1997 and 2005, a total of 3038 patients presented with STEMI and were treated with percutaneous coronary intervention (PCI). On admission 292 patients presented with cardiogenic shock. Glucose, hemoglobin and creatinine clearance were available in 183 out of 292 patients. Overall 1-year mortality was 34%. In multivariate logistic regression analysis, only glucose remained a strong independent predictor for mortality. The odds for mortality increased by 11% for each 1 mmol/l increase in glucose (OR 1.11, 95% CI 1.02-1.21, P = 0.013).

CONCLUSION
Hemoglobin and creatinine clearance bear no prognostic value. Only admission glucose levels strongly and independently predict 1-year mortality in STEMI patients with cardiogenic shock and treated with PCI.
INTRODUCTION
Nowadays, the optimal treatment for ST-segment elevation myocardial Infarction (STEMI) is rapid reperfusion, especially for patients presenting in cardiogenic shock. The SHOCK trial showed an absolute and sustained survival improvement of 13% in the early revascularization group vs. the initial medically stabilized patients. Nevertheless, cardiogenic shock remains the leading cause for in-hospital mortality in STEMI.

We recently published on independent predictors for mortality in patients with cardiogenic shock on admission. Amongst others, we demonstrated hemoglobin, glucose level and creatinine clearance on admission to be independent predictors for mortality. Although the predictive value of all three parameters has been investigated separately both in STEMI with and without cardiogenic shock, limited data are available on the predictive value of these parameters when evaluated altogether. An important purpose for our current study was, therefore, to determine and compare the predictive power of each of those measurements. Therefore the predictive value of each of these easily available laboratory measurements was investigated, when assessed simultaneously in STEMI patients presenting with cardiogenic shock on admission and treated with percutaneous coronary intervention (PCI).

METHODS
STUDY POPULATION
From January 1997 through March 2005 all consecutive STEMI patients treated with primary PCI in our hospital were entered in a dedicated database (n = 3038). A total of 292 patients (9.6%) were prospectively registered by the attending cardiologist as being in cardiogenic shock on admission. This cohort has been described before. We collected data on hemoglobin, glucose and creatinine levels on admission. Hemoglobin (Hb) data were missing in 27 patients, admission glucose levels in 39 patients and creatinine clearance (CrCl) data in 99 patients. Therefore, the cohort for the present analysis consisted of 183 STEMI patients presenting with cardiogenic shock on admission.

DATA COLLECTION AND DEFINITIONS
Baseline characteristics of the study cohort – including patient, myocardial infarcti-
on and angiographic characteristics – were retrieved from the prospectively built STEMI database. Admission laboratory data, including Hb, glucose and creatinine concentration, were collected and entered into the same database. Follow-up information was obtained at 1 and 4 years after the initial event through a written questionnaire sent to all patients. If necessary, outpatient reports were reviewed, general practitioners were contacted by telephone, or we consulted the municipal death registry. Follow-up was completed in all patients.

Anemia, according to the WHO definition, is the lower limit of a normal hemoglobin concentration: for men less than 8.1 mmol/l and for women less than 7.5 mmol/L.7,8

A fasting glucose level more than 7.0 mmol/l meets the threshold for the diagnosis of diabetes, according to the guidelines from the American Diabetes Association and the Euro Heart Survey on coronary artery disease patients with abnormal glucose regulation9,10 They defined impaired glucose tolerance as glucose levels between 6.1 and 7.0 mmol/l.

The creatinine clearance was calculated with the Cockroft–Gault equation to estimate the level of glomerular filtration rate (GFR), according to the guidelines for chronic kidney disease in adults.11 The equation calculates the creatinine clearance by the following formula: CrCl (ml/min): \[
\frac{\left(140\text{ - age}\right) \times \text{lean body weight (kg)}}{72 - \text{creatinine (mg/dl)}} \times 0.85 \text{ for women}. \]
The CrCl was found to be normally distributed and is reported in plots of 10 ml/min. The K/DOQI guidelines classify kidney function in the following manner: normal kidney function (stage I), GFR at least 90 ml/min; mild kidney dysfunction (stage II), 60–89 ml/min; and moderate to severe kidney dysfunction stage (III–V), GFR less than 59 ml/min.

In our previous studies we investigated hemoglobin, glucose levels and creatinine clearance according to the above-mentioned cut-off levels and continuous variables.4-6 However, for the purpose of this study, these three parameters were studied as a continuous variable.

Acute STEMI was defined as acute myocardial infarction with ST-segment elevation of more than 0.1 mV in two or more contiguous leads and chest pain persisting more than 30 min and less than 12 h before admission.

Cardiogenic shock was defined according to the SHOCK trial2 as a systolic blood pressure equal to or below 90 mmHg for at least 30 min or vasopressors required to
maintain blood pressure more than 90 mmHg, evidence of end-organ hypoperfusion (e.g. urine output <30 ml/h or cold, diaphoretic extremities or altered mental status) and evidence of elevated filling pressures (e.g. pulmonary congestion on examination or chest radiograph). No reflow, or not achieving thrombolysis in myocardial infarction (TIMI) 3 flow, was defined as angiographically assessed TIMI less than 3 flow after the PCI by the attending cardiologist.
Left ventricular ejection fraction (LVEF) was assessed by either echocardiography or nuclear scintigraphy, usually performed within the first week after the PCI.

**END-POINT**
The primary end-point was all-cause mortality at 1 year.

**STATISTICAL ANALYSIS**
Data were analyzed using the Statistical Package for the Social Sciences (version 11.0.1; SPSS Inc., Chicago, Illinois, USA). Continuous data are presented as mean ±SD (median and quartiles for skewed variables). Categorical data are presented as percentages. Left ventricular function was dichotomized to left ventricular ejection fraction (LVEF) less than 40% and LVEF more than 40%. Age was analyzed as a continuous variable. All P values less than 0.05 were considered statistically significant. Differences between groups were tested using the x² test for categorical variables and the two-tailed Student’s t-test for normally distributed continuous variables. Multivariate logistic regression analysis was performed to identify independent predictors for 1-year mortality. The regression model included glucose, Hb and CrCl on admission; furthermore, all variables that were significantly associated in univariate analysis or established outcome predictors, including LVEF less than 40%, age, sex, TIMI flow less than 3, the presence of multivessel disease, ischemic and door-to-balloon times and the presence of diabetes on admission were included in the model.

**RESULTS**
**BASELINE CHARACTERISTICS**
Overall 1-year mortality for the total cohort of 292 patients was 43%. This cohort of 292 patients has been described before. Baseline characteristics of the overall study cohort are displayed in Table 1.
TABLE 1 Baseline characteristics of patients with and without available biomarkers

<table>
<thead>
<tr>
<th></th>
<th>Overall cohort</th>
<th>Study cohort</th>
<th>Cohort without available markers</th>
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<tbody>
<tr>
<td></td>
<td>N = 292</td>
<td>N = 183</td>
<td>N = 109</td>
</tr>
<tr>
<td><strong>CLINICAL CHARACTERISTICS AND RISK FACTORS</strong></td>
<td></td>
<td></td>
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<tr>
<td>Age (years)</td>
<td>64 ± 13</td>
<td>63 ± 13</td>
<td>64 ± 13</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>197 (68)</td>
<td>120 (66)</td>
<td>77 (71)</td>
</tr>
<tr>
<td>Family history of CV disease (%)</td>
<td>79 (27)</td>
<td>55 (30)</td>
<td>24 (22)</td>
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<tr>
<td>Hypertension (%)</td>
<td>70 (24)</td>
<td>50 (27)</td>
<td>20 (18)</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>102 (35)</td>
<td>62 (34)</td>
<td>40 (37)</td>
</tr>
<tr>
<td>Diabetes Mellitus (%)</td>
<td>45 (15)</td>
<td>31 (17)</td>
<td>14 (13)</td>
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<tr>
<td>Hypercholesterolemia (%)</td>
<td>53 (18)</td>
<td>37 (20)</td>
<td>16 (15)</td>
</tr>
<tr>
<td>Previous myocardial infarction (%)</td>
<td>66 (23)</td>
<td>46 (25)</td>
<td>20 (18)</td>
</tr>
<tr>
<td><strong>ANGIOGRAPHIC CHARACTERISTICS</strong></td>
<td></td>
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<tr>
<td>LAD related infarction (%)</td>
<td>149 (51)</td>
<td>98 (54)</td>
<td>51 (47)</td>
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<tr>
<td>Multivessel disease (%)</td>
<td>161 (55)</td>
<td>102 (56)</td>
<td>59 (54)</td>
</tr>
<tr>
<td>TIMI 0 flow before PCI (%)</td>
<td>212 (73)</td>
<td>132 (72)</td>
<td>80 (73)</td>
</tr>
<tr>
<td>TIMI &lt;3 flow after PCI (%)</td>
<td>88 (30)</td>
<td>50 (27)</td>
<td>38 (35)</td>
</tr>
<tr>
<td>LVEF &lt;40% (%)a</td>
<td>181 (78)</td>
<td>118 (76)</td>
<td>63 (82)</td>
</tr>
<tr>
<td>Door-to-balloon time (min)</td>
<td>72 (55–108)</td>
<td>70 (53–110)</td>
<td>75 (60–104)</td>
</tr>
<tr>
<td>Total ischemic time (min)</td>
<td>159 (115–238)</td>
<td>155 (116–220)</td>
<td>162 (115–257)</td>
</tr>
<tr>
<td>IABP treatment (%)</td>
<td>173 (59)</td>
<td>124 (68)</td>
<td>49 (45)</td>
</tr>
<tr>
<td><strong>OUTCOME</strong></td>
<td></td>
<td></td>
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<tr>
<td>30-day mortality (%)</td>
<td>115 (39)</td>
<td>58 (32)</td>
<td>57 (52)</td>
</tr>
<tr>
<td>1-year mortality (%)</td>
<td>124 (43)</td>
<td>62 (34)</td>
<td>62 (57)</td>
</tr>
<tr>
<td>4-year mortality (%)</td>
<td>142 (49)</td>
<td>79 (43)</td>
<td>63 (58)</td>
</tr>
</tbody>
</table>

IABP = intra-aortic balloon pump; LAD = left anterior descending coronary artery; STEMI = ST elevation myocardial infarction; TIMI = thrombolysis in myocardial infarction; LVEF = left ventricular ejection fraction.

aMeasured in 232, 155 and 77 patients, respectively.
As said, for the purpose of the present analysis including all three laboratory measurements, the cohort consisted of 183 patients. From these 183 patients, a total of 98 (54%) patients had a LAD related infarction and 102 (56%) patients revealed multivessel disease. TIMI 3 flow was achieved in 133 (73%) patients. Left ventricular ejection fraction was assessed in 155 (85%) patients. A total of 118 patients (76%) had a LVEF less than 40%. Overall 1-year mortality was 34%. The baseline characteristics of the 183 STEMI patients with cardiogenic shock on admission and treated with PCI are detailed in Table 1. Baseline characteristics of patients who were not included in the present study are displayed in Table 1 as well. Mortality rates at 30 days, 1 year and 4 years were significantly higher in patients who were not included in the study cohort. In addition, the percentage of patients receiving intra-aortic balloon pump (IABP) support was significantly higher in the study cohort. No further differences were demonstrated between groups.

Multivariate analysis showed that from the studied biochemical parameters, only admission glucose remained a strong and independent predictor for 1-year mortality. Even after correction for age, no-reflow and LVEF less than 40%, the odds for mortality increased by 11% for every 1 mmol/l increase in glucose concentration on admission (OR 1.11, 95% CI 1.02–1.21, P = 0.013) (Table 2).

**DISCUSSION**

**PLASMA GLUCOSE**

The main finding of this study is that, upon evaluation of the predictive value of glucose levels, Hb and CrCl on admission, glucose level on admission is the only independent predictor of mortality in STEMI patients complicated with cardiogenic shock and treated with primary PCI. In our previous studies, we demonstrated the predictive value of glucose levels, Hb concentration and calculated CrCl on admission. When studied separately, each of these parameters was demonstrated to independently predict 1-year mortality, after adjustment for several established mortality predictors such as age, LVEF, TIMI flow less than 3 and the presence of multivessel disease. Several other studies have demonstrated the prognostic value of each of these parameters, in STEMI both with and without cardiogenic shock. However, as limited data were available on the predictive value of each of these parameters in direct comparison, in the current study we mainly sought to compare the
Upon multivariate analysis, glucose on admission was the only laboratory measurement that independently predicted 1-year mortality, as opposed to Hb and CrCl.

The question that subsequently arises is whether hyperglycemia on admission results from an acute-phase reaction in patients with a poor condition, which may partly be due to lower Hb levels or CrCl, or whether it is an underlying disturbance in the glucose metabolic pathway that renders patients at high risk.

First, one might speculate that hyperglycemia is only an utterance of stress and the resultant of an acute-phase reaction in the clinical entity of an acute myocardial infarction with or without cardiogenic shock, the so called stress hyperglycemia. The release of stress hormones, such as cortisol, epinephrine and norepinephrine, which is activated by the low-output state in STEMI complicated by cardiogenic shock, has

### TABLE 2 Results of multivariate logistic regression analysis

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission glucose concentration&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.111</td>
<td>1.023 – 1.208</td>
<td>0.013</td>
</tr>
<tr>
<td>Admission hemoglobin concentration&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.992</td>
<td>0.992 – 1.423</td>
<td>NS</td>
</tr>
<tr>
<td>Admission Cr Clearance&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.001</td>
<td>0.989 – 1.013</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.401</td>
<td>0.438 – 4.488</td>
<td>NS</td>
</tr>
<tr>
<td>Age</td>
<td>1.066</td>
<td>1.018 – 1.117</td>
<td>0.006</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.353</td>
<td>0.494 – 3.705</td>
<td>NS</td>
</tr>
<tr>
<td>Total ischemic time</td>
<td>1.003</td>
<td>1.000 – 1.007</td>
<td>NS</td>
</tr>
<tr>
<td>Door-to-balloon time</td>
<td>1.004</td>
<td>0.998 – 1.011</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF less than 40%</td>
<td>20.537</td>
<td>2.494 – 169.112</td>
<td>0.005</td>
</tr>
<tr>
<td>TIMI flow less than 3</td>
<td>1.510</td>
<td>0.574 – 3.973</td>
<td>NS</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>1.039</td>
<td>0.371 – 2.916</td>
<td>NS</td>
</tr>
</tbody>
</table>

Cr=creatinine; LVEF=left ventricular ejection fraction; TIMI=thrombolysis in myocardial infarction.

<sup>a</sup>For admission glucose concentration (mmol/L) and hemoglobin (mmol/L) the odds ratio is noted per continue variable per mmol/L. <sup>b</sup>For admission Creatinine Clearance (ml/min) the odds ratio is noted per 10 ml/min of clearance. Significant predictors are in bold.
been demonstrated to be an important determinant of stress hyperglycemia. Cortisol has three major vital functions. In addition to raising blood pressure and its immunosuppressive effect, it also raises glucose levels. In addition, higher glucose levels may arise from increased glycogenolysis in the liver and mobilization of amino acids for glucose metabolism.\textsuperscript{19}

However, an underlying defect in glucose metabolism may play a role as well. However, whether all hyperglycemic STEMI patients actually have diabetes or disturbed glucose tolerance after the initial acute event is the subject of ongoing investigation. It has been shown that some of the hyperglycemic patients do not have persistent disturbed glucose metabolism after the initial event. It is unknown whether this also occurs after STEMI with cardiogenic shock. Hyperglycemia may, in fact, only or mainly be present in the acute phase of STEMI. Yet another unanswered question is whether patients who have hyperglycemia in the acute phase are more prone to develop hyperglycemia during another acute (ischemic) event.

In addition to the stress hyperglycemia, long-lasting hyperglycemia, potentially due to an underlying defect in glucose metabolism, could play a role in the process of atherosclerosis, resulting in a more extensive coronary artery disease. Pre-existing diastolic and systolic dysfunction as an extension of the diffusely endothelial dysfunction in addition to the ischemic heart may result in a worse outcome.

**SECONDARY EFFECTS OF HYPERGLYCEMIA**

Hyperglycemia has prothrombotic and proinflammatory effects. Thrombus locked in the microvasculature may lead to accelerated remodeling of the surrounding myocardium and less collateral vascular development.\textsuperscript{20} Furthermore, recovery of stunned myocardium can be more difficult for cells in an environment of hyperglycemia, as hyperglycemia has been demonstrated to be associated with several markers for left ventricular dysfunction.\textsuperscript{21,22} In nondiabetic patients, abnormal HbA1c results showed a higher mortality.\textsuperscript{23}

We are currently investigating whether patients who were admitted with STEMI and cardiogenic shock and survived, still have disturbed glucose tolerance testing after more than 1 year (OMIGOT pilot study). This will provide important insight into the fact whether in this patient population hyperglycemia is more a tempora-
ry phenomenon (stress) or whether even after the initial event, it was a predictor of latent glucose metabolism disturbance.

**CLINICAL IMPLICATIONS**

Our findings emphasize the importance of hyperglycemia on admission as an easily available diagnostic tool for risk stratification. In addition, it may be an important therapeutic target. Several studies have been conducted to evaluate glucose-lowering strategies in STEMI patients, including the infusion of glucose-insulin-potassium and sole insulin. Although results from many of those studies have been somewhat disappointing so far, this may have been due to the fact that actual glucose lowering did not take place. Therefore, additional studies with more strict glucose lowering regimens may be needed to more adequately assess the usefulness of glucose-lowering therapy.

**LIMITATIONS**

There are several important limitations to this study. First of all, it is a single-center population-based investigation. However, it reflects a representative population as it comprises a rather homogeneous population over a wide range of years (1997–2005). In addition, it was not possible to assess the rate of undiagnosed diabetes or impaired glucose tolerance in our study population; fasting plasma glucose, glucose levels following oral glucose tolerance testing or HbA1c on admission were not routinely measured. Finally, selection bias plays a role, as patients without available admission laboratory data were excluded from the study cohort. Patients in whom blood sampling was not performed may have been in a worse baseline clinical condition, which is also reflected by the higher mortality rates when compared to the study cohort. This could be a partial explanation for the relatively low overall mortality (34%) in the present study cohort of cardiogenic shock patients opposed to other studies. Additionally, the present cohort is in itself a subgroup of the previously described larger cohort with a mortality rate of 42%. However, these results are an expression of the adoption of primary PCI as the therapy of choice for all STEMI patients since 1997 in our hospital, confirming the trend towards improved survival for cardiogenic shock patients with increasing primary PCI rates.
Conclusion

Admission glucose level only and not hemoglobin or renal function predicts 1-year mortality in patients with STEMI complicated with cardiogenic shock and treated with PCI. The previously identified predictors, hemoglobin levels and creatinine clearance in the same cohort, bear no predictive value after adjusting for glucose levels. Further studies are warranted to determine whether concomitant strict glycometabolic regulation in STEMI patients treated with PCI, particularly those with cardiogenic shock patients, will improve clinical outcome. A long-term follow-up study on the mechanism of stress hyperglycemia in survivors of STEMI with cardiogenic shock is currently ongoing.
REFERENCES


