

Diabetes & Vascular Disease Research

DECEMBER 2007 - REPRINT

VOLUME 4 ISSUE 4

ORIGINAL ARTICLE

Admission glycaemia and outcome in patients with acute coronary syndrome

*Damaris Müdespacher, Dragana Radovanovic,
Edoardo Camenzind, Manfred Essig, Osmund Bertel,
Paul Erne, Franz Robert Eberli, Felix Gutzwiller on
behalf of the Amis plus investigators*

Admission glycaemia and outcome in patients with acute coronary syndrome

DAMARIS MÜDESPACHER, DRAGANA RADOVANOVIC, EDOARDO CAMENZIND, MANFRED ESSIG, OSMUND BERTEL, PAUL ERNE, FRANZ ROBERT EBERLI, FELIX GUTZWILLER ON BEHALF OF THE AMIS PLUS INVESTIGATORS

Abstract

Some studies of patients with acute myocardial infarction have reported that hyperglycaemia at admission may be associated with a worse outcome. This study sought to evaluate the association of blood glucose at admission with the outcome of unselected patients with acute coronary syndrome (ACS).

Using the Acute Myocardial Infarction and unstable angina in Switzerland (AMIS Plus) registry, ACS patients were stratified according to their blood glucose on admission: group 1: 2.80–6.99 mmol/L, group 2: 7.00–11.09 mmol/L and group 3: ≥ 11.10 mmol/L. Odds ratios for in-hospital mortality were calculated using logistic regression models.

Of 2,786 patients, 73% were male and 21% were known to have diabetes. In-hospital mortality increased from 3% in group 1 to 7% in group 2 and to 15% in group 3. Higher glucose levels were associated with larger enzymatic infarct sizes ($p < 0.001$) and had a weak negative correlation with angiographic or echographic left ventricular ejection fraction. High admission glycaemia in ACS patients remains a significant independent predictor of in-hospital mortality (adjusted OR 1.08; 95% confidence

intervals [CI] 1.05–1.14, $p < 0.001$) per mmol/L. The OR for in-hospital mortality was 1.04 (95% CI 0.99–1.1; $p = 0.140$) per mmol/L for patients with diabetes but 1.21 (95% CI 1.12–1.30; $p < 0.001$) per mmol/L for non-diabetic patients.

In conclusion, elevated glucose level in ACS patients on admission is a significant independent predictor of in-hospital mortality and is even more important for patients who do not have known diabetes.

Diabetes Vasc Dis Res 2007;4:346–52

doi:10.3132/dvdr.2007.063

Key words: acute coronary syndrome, admission glycaemia, diabetes, gender, hyperglycaemia, outcome.

Introduction

Diabetes mellitus is associated with an increased risk of cardiovascular morbidity and mortality.^{1,2} Findings of a meta-regression analysis suggest that even blood glucose levels below the threshold for diabetes are related to raised cardiovascular risk.³ Patients with a longer duration of diabetes more frequently show signs of diabetic neuropathy that can result in atypical symptoms during myocardial infarction. Thus, diagnosis of an acute coronary syndrome (ACS) is more difficult in these patients and initiation of adequate therapy is often delayed.⁴ Among patients with acute myocardial infarction (AMI), diabetes mellitus is associated with higher mortality rates, both in-hospital^{5,6} and during long-term follow-up.^{5,7} This is the case across the whole spectrum of ACS.⁸ In that study, ACS patients with diabetes had a higher risk of both death and re-infarction at 30 days than those without diabetes, and the rates of death or re-infarction at six months remained higher in the diabetic group, whether they presented with ST-elevation myocardial infarction (STEMI) or non-ST-elevation myocardial infarction (NSTEMI).

High blood glucose levels in patients admitted for ACS/AMI are common and are associated with an increased risk of death in both patients with diabetes^{9–19} and patients without diabetes.^{9–17,19} Admission hyperglycaemia is an even stronger predictor for mortality in patients without a medical history of diabetes.^{9,13,19}

However, there is little information about differences in outcome between men and women with hyperglycaemia on admission for ACS/AMI. The aim of our study was to investigate the association of admission glycaemia and outcome in

Acute myocardial infarction and unstable angina in Switzerland (AMIS Plus) Data Center, Institute of Social and Preventive Medicine, University of Zurich, Zurich, Switzerland.

Damaris Müdspacher, Doctoral Medical Student

Dragana Radovanovic, Head of AMIS Plus Data Center

Division of Cardiology, University Hospital, Geneva, Switzerland.

Edoardo Camenzind, Associate Professor

Department of Medicine, Hospital Zweisimmen, Zweisimmen, Switzerland.

Manfred Essig, Head of Internal Medicine

Division of Cardiology, Stadtspital Triemli, Zurich, Switzerland.

Osmund Bertel, Professor of Medicine, Head of Cardiology

Division of Cardiology, Kantonsspital, Lucerne, Switzerland.

Paul Erne, Professor of Medicine, Head of Cardiology

Division of Cardiology, University Hospital, Zurich, Switzerland.

Franz Robert Eberli, Associate Professor of Medicine

Institute of Social and Preventive Medicine, University of Zurich, Zurich, Switzerland.

Felix Gutzwiller, Professor of Medicine, Director of Institute

Correspondence to: Dr Dragana Radovanovic

AMIS Plus Data Center, Institute of Social and Preventive Medicine,

University of Zurich, Hirschengraben 84, 8001 Zurich, Switzerland.

Tel: +41 044 634 48 34; Fax: +41 044 634 49 86

E-mail: dragana@ifspm.uzh.ch

Table 1. Baseline characteristics and outcome of all ACS patients according to admission glycaemia groups

| Glucose levels (mmol/L) | G1: 2.80–6.99 | G2: 7.00–11.09 | G3: ≥ 11.10 | p values |
|---|------------------|------------------|----------------|----------|
| Number of patients (n=2,786) | 1,299 | 1,117 | 370 | |
| Glycaemia on admission (mmol/L) | | | | |
| mean (SD) | 5.9 (0.7) | 8.4 (1.1) | 15.4 (4.5) | 0.001 |
| median | 6.0 | 8.2 | 13.7 | |
| Age min - max | 28–95 | 27–96 | 37–93 | 0.01 |
| mean ± SD | 65 (13) | 67 (13) | 69 ± 13 | |
| median | 65 | 68 | 71 | |
| Sex male (%) | 993/1,299 (76.4) | 795/1,117 (71.2) | 252/370 (68.1) | |
| female (%) | 306/1,299 (23.6) | 322/1,117 (28.8) | 118/370 (31.9) | 0.001 |
| Past medical history | | | | |
| Hypertension (%) | 728/1,259 (57.8) | 661/1,074 (61.5) | 267/354 (75.4) | < 0.001 |
| Dyslipidaemia (%) | 679/1,162 (58.4) | 567/991 (57.2) | 206/332 (62.0) | 0.306 |
| Smoking (current) (%) | 477/1,246 (38.3) | 342/1,042 (32.8) | 106/329 (32.2) | 0.011 |
| Obesity (BMI ≥ 30 kg/m ²) (%) | 194/1,151 (16.9) | 219/999 (21.9) | 83/305 (27.2) | < 0.001 |
| Co-morbidities | | | | |
| Moderate-to-severe renal disease (%) | 72/1,273 (5.7) | 95/1,080 (8.8) | 50/362 (13.8) | < 0.001 |
| Diabetes (%) | 114/1,299 (8.8) | 215/1,117 (19.2) | 244/370 (65.9) | < 0.001 |
| Delay in minutes (median, interquartile range) | 255 (120, 810) | 210 (110, 600) | 210 (103, 770) | 0.013 |
| | (n=1,007) | (n=926) | (n=278) | |
| CPR (%) | 10/1,251 (0.8) | 17/1,076 (1.6) | 32/347 (9.2) | < 0.001 |
| Killip class III/IV (%) | 24/1,297 (1.9) | 53/1,109 (4.8) | 63/365 (17.3) | < 0.001 |
| Symptoms on admission | | | | |
| Atypical (%) | 136/1,277 (10.6) | 145/1,097 (13.2) | 75/359 (20.9) | < 0.001 |
| STEMI (%) | 615/1,298 (47.4) | 689/1,117 (61.7) | 215/370 (58.1) | < 0.001 |
| Angiographic findings | | | | |
| Three-vessel disease (%) | 300/985 (30.5) | 277/848 (32.7) | 89/230 (38.7) | 0.053 |
| Insulin (during initial treatment) (%) | 93/1,277 (7.3) | 176/1,084 (16.2) | 208/364 (57.1) | < 0.001 |
| Reperfusion | | | | < 0.001 |
| Thrombolysis (%) | 40/1,281 (3.1) | 42/1,110 (3.8) | 9/369 (2.4) | |
| PCI primary (%) | 772/1,281 (60.3) | 729/1,110 (65.7) | 188/369 (50.9) | |
| Outcome | | | | |
| MACE | 4.9 | 10.1 | 18.7 | < 0.001 |
| In-hospital mortality | 2.6 | 7.3 | 14.9 | < 0.001 |

Key: CPR = cardiopulmonary resuscitation; STEMI = ST segment elevation myocardial infarction; PCI = percutaneous coronary intervention; MACE = major adverse cardiac events; BMI = body mass index

patients admitted for ACS; furthermore, to examine if there are differences in outcome not only between patients with and without diabetes, but also between men and women with hyperglycaemia at hospital admission.

Patients and methods

The AMIS Plus Registry

In 1997, the Swiss Societies of Cardiology, Internal Medicine and Intensive Care initiated a nationwide prospective registry to assess the diagnostic and therapeutic measures for patients with AMI in Switzerland (AMIS). Academic and non-academic hospitals participate voluntarily and provide blinded data on these patients to the AMIS Plus Data Center through an internet- or paper-based questionnaire of 140 questions. The Data Center controls and checks the data for plausibility and cross-checks in case of queries. In the year 2000, patients with unstable angina were added to the registry. AMIS Plus is an industry-sponsored project, but the

supporting institutions do not play any role in the design of the registry, data collection, analysis or interpretation. The project is led by a Steering Committee comprised of members of the founding societies. The registry was approved by the Over-regional Ethical Committee for Clinical Studies and the Swiss Board of Data Security.^{20,21} In March 2005 the AMIS Plus Questionnaire was revised and admission glycaemia was included.

Patients

Patients enrolled in the AMIS Plus registry from March 2005 to March 2006 across the whole spectrum of ACS and with valid data both on glycaemia at admission and history of diabetes were included. The spectrum covered AMI, defined by characteristic symptoms and/or ECG changes and enzymes (total creatine kinase [CK] or creatine kinase MB fraction greater than twice the upper limit of normal), minimal necrosis (the same, but the enzymes below twice the

Table 2. Predictors of in-hospital mortality at admission by logistic regression analysis in patients with ACS (n=2,525)

| | Odds ratio | 95% CI | Significance |
|------------------------------------|------------|------------|--------------|
| Glucose levels per mmol/L | 1.08 | 1.05–1.14 | 0.001 |
| Age per year | 1.07 | 1.05–1.10 | <0.001 |
| Gender | 0.84 | 0.55–1.27 | 0.399 |
| History of diabetes | 0.86 | 0.53–1.39 | 0.545 |
| History of arterial hypertension | 0.89 | 0.72–1.75 | 0.602 |
| Renal disease | 2.23 | 1.38–3.62 | 0.001 |
| Killip class II | 1.57 | 0.99–2.49 | 0.056 |
| Killip class III | 1.83 | 0.88–3.82 | 0.106 |
| Killip class IV | 6.11 | 2.73–13.65 | <0.001 |
| STEMI | 1.78 | 1.19–2.66 | 0.005 |
| CPR | 6.49 | 2.88–14.61 | <0.001 |
| Heart rate | 1.00 | 0.99–1.01 | 0.553 |
| Systolic blood pressure | 0.98 | 0.97–0.99 | <0.001 |
| Percutaneous coronary intervention | 0.47 | 0.30–0.75 | 0.002 |

Key: CI = confidence intervals; ACS = acute coronary syndromes; STEMI = ST segment elevation myocardial infarction; CPR = cardiopulmonary resuscitation

upper limit of normal and troponin-positive) and unstable angina (symptoms and/or ECG typical for ACS, normal enzymes). Patients were defined as diabetic when diabetes mellitus was reported in their past medical history, independent of the kind of treatment they were receiving (oral agents, insulin-treated or untreated). Co-morbidities were documented using the Charlson Comorbidity Index.²² Other risk factors previously diagnosed, treated and/or documented in the patients' medical history were also identified. Patients were stratified into three admission glycaemia groups: normal (G1: 2.80–6.99 mmol/L), intermediate (G2: 7.00–11.09 mmol/L) and elevated glucose concentrations (G3: \geq 11.10 mmol/L). Baseline characteristics and outcome were compared between these three groups. Within G3 we compared short-term outcome of diabetic versus non-diabetic patients and of male versus female ACS patients. The end point was set as major adverse cardiac events (MACE), including re-infarction, stroke and death or in-hospital mortality.

Statistical analyses

Data are presented as percentages for discrete variables and as means (SD) and/or medians with interquartile range for continuous variables. Differences in baseline characteristics were compared using the *t*-test and the chi-squared test. A *p* value <0.05 was considered statistically significant.

Logistic regression models for predicting in-hospital mortality were conducted using the Enter method with the following variables: age, gender, history of diabetes mellitus, hypertension and renal disease, cardiopulmonary resuscitation (CPR), Killip class, STEMI, systolic blood pressure, heart

rate on admission and primary percutaneous coronary intervention (PCI).

SPSS (Chicago, III, US) for Windows XP (version 13.0) was used for all statistical analyses.

Results

Overall patient population

Of 2,924 ACS patients, 2,790 cases met the inclusion criteria. Four patients with hypoglycaemia at admission (< 2.80 mmol/L) were excluded because the numbers were so small. Of the remaining 2,786 cases, 2,040 (73%) were male and 746 (27%) female, 573 (21%) were known to have diabetes and 2,213 (79%) were non-diabetic or their diabetes status was unknown.

At hospital admission, the majority of ACS patients (47%) had normal glucose levels (2.80–6.99 mmol/L, G1), 40% intermediate levels (7.00–11.09 mmol/L, G2) and 13% had clearly elevated glucose levels (\geq 11.10 mmol/L, G3). Patient characteristics for the three groups are shown in table 1. Patients with increased glucose levels were more often diabetic. They were older, more likely to be female and obese, and more often had a past medical history of arterial hypertension and moderate-to-severe renal disease. The frequencies of a past medical history of dyslipidaemia were similar in all three groups. The delay from onset of symptoms to hospitalisation tended to be longest in G1. Patients in G3 needed CPR more often prior to arrival at hospital, and presented more often with Killip classes III/IV and atypical symptoms compared to G1 and G2, respectively. Patients in G2 and G3 suffered a STEMI more often than patients in G1. Those in G1 were more likely to be current smokers. There was a tendency towards a greater number of patients with

three-vessel disease in G3. G3 patients also received insulin within 24 hours of admission more often compared to G1 and G2, respectively. G3 patients experienced more strokes and cardiogenic shocks, whereas the frequencies of re-infarction were similar in the three groups. The major adverse cardiac events (MACE) rate was higher in G2 (10%) and G3 (19%) compared with G1 (5%). Overall in-hospital mortality was 6%, with differences among the groups: 3% in G1, 7% in G2 and 15% in G3.

Diabetics versus non-diabetics

Overall in-hospital mortality was 10% in all diabetic patients and 5% in all non-diabetic patients ($p < 0.001$). Of the patients with admission glycaemia ≥ 11.10 mmol/L, 66% had a previous diagnosis of diabetes and 34% did not. In this hyperglycaemic group (G3), patients with previously diagnosed diabetes were older (70 ± 12 vs. 68 ± 14 years; $p < 0.001$), had significantly more risk factors such as arterial hypertension (84% vs. 59%, $p < 0.001$), dyslipidaemia (72% vs. 45%, $p < 0.001$) and obesity (32% vs. 18%, $p = 0.009$), but tended to be current smokers less often than non-diabetic patients (29% vs. 39%, $p = 0.0065$). Diabetic patients were more often found to have three-vessel coronary artery disease (45% vs. 27%, $p = 0.007$) and previous coronary artery bypass grafting (CABG; 9% vs. 3%, $p = 0.034$) than non-diabetics.

The delay from onset of symptoms to hospitalisation was longer in diabetic than in non-diabetic patients (270 minutes; interquartile range 115–810 vs. 180 minutes; interquartile range 97–379 minutes, $p = 0.044$), but there was no difference in the frequency of atypical symptoms on admission. Non-diabetics needed CPR significantly more often prior to arrival at hospital (14% vs. 7%, $p = 0.030$). They tended to experience a STEMI more often (65% vs. 55%, $p = 0.096$) and to be admitted in heart failure Killip class III/IV (23% vs. 15%, $p = 0.058$). Reperfusion rates (thrombolysis and primary percutaneous coronary intervention; PCI) were similar, but patients without diabetes received insulin significantly less frequently as part of the initial treatment compared to patients with diabetes (29% vs. 72%, $p < 0.001$). In patients without diabetes, the hospital course was complicated more often by cardiogenic shock than in patients with diabetes (15% vs. 7%; $p = 0.020$). The frequency of re-infarction and cerebrovascular insult was similar between diabetic and non-diabetic patients. Non-diabetics with admission glycaemia ≥ 11.10 mmol/L had a non-significantly higher MACE rate (25% vs. 16%; $p = 0.053$) and in-hospital mortality (20% vs. 12%; $p = 0.064$) compared to diabetic patients.

Female versus male patients

Overall, in-hospital mortality was 6% in all men and 8% in all women ($p = 0.075$). Of the patients with admission glycaemia ≥ 11.10 mmol/L, 252 (68%) were male and 118 (32%) female. The mean glucose levels were similar in both genders (15.3 mmol/L vs. 15.5 mmol/L, $p = 0.821$) while male patients were on average eight years younger than female patients (67 vs. 75 years, $p < 0.001$). Frequency of history of diabetes was similar in both genders (65% vs. 69%, $p = 0.482$) while female patients tended to have moderate-

to-severe renal disease more often (19% vs. 12%, $p = 0.074$). Males had significantly less arterial hypertension (70% vs. 86%, $p = 0.001$) as a risk factor, but were more often current smokers (40% vs. 15%, $p < 0.001$) and overweight (77% vs. 60%, $p = 0.004$) and more frequently had a history of CABG (10% vs. 2%, $p = 0.004$). The proportion with a history of dyslipidaemia (63% vs. 59%, $p = 0.541$) was similar in both genders. In females, the delay from onset of symptoms to hospitalisation was about twice as long as in males (358 minutes; interquartile range 120–939 minutes vs. 180 minutes; interquartile range 96–642 minutes, $p < 0.001$), and they tended to have atypical symptoms more often (27% vs. 18%, $p = 0.071$) on admission. Male patients tended to present more often with STEMI (61% vs. 52%, $p = 0.091$) and needed CPR significantly more frequently prior to arrival at hospital (13% vs. 2%, $p = 0.001$). Heart failure on admission (Killip class III/IV) and complications (cardiogenic shock, re-infarction and cerebrovascular insult) were, however, similar in both male and female patients. Although males received insulin significantly more often as immediate medication (61% vs. 49%, $p = 0.031$) and underwent primary PCI more frequently (57% vs. 39%, $p = 0.10$), they had a significantly worse outcome. Male patients had a higher MACE rate (23% vs. 11%; $p = 0.014$) and higher in-hospital mortality (18% vs. 8%; $p = 0.007$) than females.

Glucose levels and infarct size

There was a highly significant, but weak, positive correlation between glucose levels and maximum CK levels during hospitalisation ($n = 2,747$, correlation coefficient 0.18, $p < 0.001$), a weak negative correlation between glucose levels and angiographic left ventricular ejection fraction (LVEF; $n = 1,684$, correlation coefficient -0.16, $p < 0.001$) and a weak negative correlation between glucose levels at admission and echographic LVEF ($n = 1,084$, correlation coefficient -0.27, $p < 0.001$).

Predictors of in-hospital mortality at admission by logistic regression analysis in ACS patients

In multivariate logistic regression analysis, higher admission glycaemia remained an independent predictor of in-hospital mortality (table 2). The unadjusted OR for in-hospital mortality for glucose levels was 1.14 (95% CI 1.12–1.18) per mmol/L, and adjusted OR was 1.08 (95% CI 1.05–1.14, $p < 0.001$). The OR for in-hospital mortality was 1.04 (0.99–1.1; $p = 0.140$) per mmol/L for diabetic patients but 1.21 (1.12–1.30; $p < 0.001$) per mmol/L for non-diabetic patients; and 1.07 (0.97–1.15; $p = 0.109$) for female patients and 1.11 (1.05–1.17; $p < 0.001$) for male patients.

Discussion

The results of this study showed that patients presenting with an ACS who are hyperglycaemic on admission represent a high-risk population, even in the absence of an established diagnosis of diabetes. Abnormal glucose metabolism during the acute phase of AMI or ACS is common, and admission hyperglycaemia is associated with increased short-term mortality in both diabetic^{11-13,17-19} and non-diabetic^{11-13,17,19} patients. Moreover, short-term mortality is predicted even more

powerfully by admission hyperglycaemia in patients without known diabetes.^{13,19}

In-hospital mortality rates of all ACS patients in G1 (3%), G2 (7%), and G3 (15%) in our study are in line with those from another study that investigated the association of glycaemia on admission and outcome in patients admitted for AMI (< 7.8 mmol/L: 1%, 7.8–11 mmol/L: 6%, > 11 mmol/L: 17%).¹⁷ Further, in-hospital mortality rates of diabetic (12%) and non-diabetic patients (20%) in G3 are similar to those observed by Wahab¹⁹ (diabetic > 11 mmol/L: 19%; non-diabetic > 11 mmol/L: 24%).

In our study, increased glucose levels at admission in ACS patients were associated with an increase of in-hospital mortality of 8% per mmol/L, even after adjustment for covariables. The impact of an elevated admission glucose level on in-hospital mortality was even more important for non-diabetic than for diabetic ACS patients (interaction between glucose levels and history of diabetes OR=0.87; 95% CI 0.79–0.94). Similarly, 30-day mortality was predicted by baseline glucose with a hazard ratio of 1.12 per 0.6 mmol/L increase in patients without diabetes, but not in those with diabetes.¹³ In addition, several studies have shown that hyperglycaemia on admission is associated with long-term mortality after AMI or ACS in both patients with^{9,10, 13–19} and without^{9, 10, 13–17, 19} previously known diabetes.

There are several possible causes of hyperglycaemia on admission in patients with ACS, but it is not clear why it should be associated with poor outcome. First, hyperglycaemia on admission in non-diabetic ACS patients might represent previously undiagnosed diabetes or pre-existing impaired glucose tolerance. Wahab¹⁹ suggested that in non-diabetic AMI patients, hyperglycaemia probably represents unrecognised and therefore untreated diabetes, with many years of uncontrolled elevated blood glucose levels resulting in increased endothelial damage and thus greater risk for macro- and micro-vascular morbidity. However, Tenerz²³ found that in non-diabetic patients with AMI, increased blood glucose on admission was not a reliable method of establishing a diagnosis of diabetes and follow-up was necessary. Nevertheless, a substantial proportion of the non-diabetic patients with even only slightly elevated admission glycaemia (< 11.10 mmol/L) have undiagnosed diabetes or impaired glucose tolerance,²⁴ thus bearing an increased risk of poor outcome after AMI/ACS.^{5–8}

Secondly, hyperglycaemia on admission in ACS patients might represent a response to acute and severe stress¹¹ whereas increased catecholamine levels result in decreased insulin secretion and increased insulin resistance. In the CARDINAL study,¹³ individuals with higher baseline glucose (upon diagnosis of AMI) had larger infarct sizes, determined by CK-MB area under the curve. In the Zwolle trial²⁵ there was a clear association between LVEF, measured by equilibrium radionuclide ventriculography, and glucose levels in non-diabetic patients with myocardial infarction. Higher glucose levels on admission were correlated with lower LVEF. These findings suggest that high glucose levels on admission might be a marker of large myocardial infarctions and therefore also reflect severe stress and a high risk of poor prognosis. In our study, there was a significant positive correlation

between glucose levels and infarct size, measured as maximum CK, and a negative correlation between glucose levels and LVEF measured on angiography and echocardiography.

In the DIGAMI study,¹⁴ glycosylated haemoglobin, body weight, heart rate and pulmonary rates on admission were independently linked to admission hyperglycaemia. These factors might reflect both previously unrecognised diabetes and severe stress during the acute phase of AMI.

In this study, CPR prior to arrival at hospital might have played an important role in the clinical course of ACS. Of all ACS patients, the highest frequencies of CPR were found in G3 (in non-diabetics and in males). Hyperglycaemia in these patients could have been a result of CPR and would therefore represent severe stress. However, it is also possible that hyperglycaemia itself led to a worse clinical course and cardiac arrest in the acute phase of ACS, necessitating CPR. Since autonomic neuropathy in diabetic patients may mask ACS, a larger proportion of hyperglycaemic diabetic patients than hyperglycaemic patients without diabetes might have died at home. However, if a high proportion of non-diabetic hyperglycaemic patients were in fact undiagnosed (and therefore untreated) diabetic patients, this might explain why they needed CPR significantly more often prior to arrival at hospital and why their hospital course was complicated more often by cardiogenic shock. It remains unclear whether hyperglycaemia is simply a marker of stress and of poor prognosis or whether hyperglycaemia predisposes to a worse outcome.⁹

In view of all these results, admission hyperglycaemia in non-diabetics during the acute phase of ACS and its association with poor outcome represents most likely a combination of previously undiagnosed diabetes, impaired glucose tolerance, and a response to acute and severe stress.¹¹

In ACS, STEMI has a higher mortality rate than NSTEMI. In our study, patients with intermediate and high glucose levels presented more often with STEMI than NSTEMI, and non-diabetic males in G3 had the highest rate of STEMI, which could have contributed to their poor outcome. Outcome in STEMI is improved by reperfusion therapy, with a significant benefit for primary PCI over fibrinolysis.^{13, 26–28} In this study, patients in G3 received primary PCI significantly less frequently than those in G1 and G2, which might have contributed to the worse outcome in this group. These findings are in accordance with those of Straumann,¹⁷ who found that in patients treated with PCI during the first 24 hours of an AMI, glucose levels > 11.0 mmol/L were a strong predictor of 30-day mortality even after adjustment for age, cardiogenic shock (Killip class IV), and TIMI 3 flow after PCI. There was no evidence of a different effect of glucose levels on survival between patients with and without cardiogenic shock (Killip class IV) on admission.

The DIGAMI study showed that immediate insulin-glucose infusion followed by multi-dose subcutaneous insulin reduced one-year mortality significantly in patients with AMI and admission blood glucose concentrations > 11.0 mmol/L, although the effect of this treatment on in-hospital mortality was not significant.²⁹ The second DIGAMI study did not support this. However, compared to the first DIGAMI trial, overall long-term glucose control was better in the second

DIGAMI trial, which may have had a favourable influence on outcome in the latter.³⁰

Published risk score models for ACS to identify patients at high risk for death and other major cardiac ischaemic events have included a medical history of diabetes as a categorical variable.^{31,32} Straumann¹⁷ has stated that the categorical variable 'elevated admission blood glucose level' would be a more powerful predictor of outcome than the variable 'medical history of diabetes' in a modified risk score for patients with ACS.

There is little published information on the differences in outcome between men and women with hyperglycaemia at the time of admission for ACS. In the DIGAMI study, there was no significant difference in long-term mortality between male and female patients admitted for AMI with glycaemia ≥ 11.0 mmol/L, and female sex was not an independent, unfavourable prognostic factor.¹⁵ In our study, overall in-hospital mortality tended to be higher in women than in men ($p=0.075$), while among the patients with admission glycaemia > 11.10 mmol/L, the MACE rate and in-hospital mortality were significantly higher in men than in women, even though men received primary PCI and insulin significantly more often as immediate medication, and women were older and had a history of hypertension more frequently. In males, but not in females, increased glucose levels at admission were associated with significant increases of in-hospital mortality of 11% per mmol/L even after adjusting for covariables. However, gender was not an independent predictor of in-hospital mortality in multivariate logistic regression analysis.

Detection of high-risk patients by applying reliable screening methods to all patients at admission for ACS is indispensable in order to ensure rapid and appropriate treatment and, consequently, decreased in-hospital mortality. Our study has shown that hyperglycaemia on admission is a strong risk factor for worse outcome in all patients admitted with ACS. Measurement of glycaemia at hospital admission may therefore be used as an early screening method to detect high-risk patients. Blood glucose concentrations are available within minutes of presentation, at a time when other elements of risk prediction models such as elevated serum markers of myocardial necrosis^{17,31,32} may still be normal. According to diabetes guidelines, all patients with coronary artery disease and unknown diabetes status should be screened for type 2 diabetes by an oral glucose tolerance test (OGTT) that gives both fasting and two-hour post-load glucose values, and by measuring HbA_{1C}.³³ In patients admitted for ACS with significantly elevated blood glucose levels, normoglycaemia should be aimed for as soon as possible by means of insulin infusion.

Glucose levels at admission for ACS could therefore be used in order to detect high-risk individuals and to treat them adequately. In order to detect diabetes or impaired glucose homeostasis and therefore to prevent re-infarction or death during follow-up, these screening methods could be applied at discharge.

Study limitations

Differences in the use of drugs (aspirin, statins, β -blockers

and angiotensin-converting enzyme [ACE] inhibitors) are known to influence the outcome of acute myocardial infarction and might have played a role in the effect on MACE and the in-hospital mortality rate.³⁴ In this study, we did not analyse the influence of these drugs on MACE or on the in-hospital mortality rate.

Since we did not measure HbA_{1C} at admission or fasting glucose after recovery, we were unable to tell whether hyperglycaemia at admission was caused by previously undiagnosed diabetes or by severe stress during the acute phase of ACS. We used the medical history to determine a previous diagnosis of diabetes mellitus, thus it is likely that some 'non-diabetics' had unrecognised diabetes mellitus.

It has recently been shown that there is a U-shaped relationship between admission blood glucose levels and poor outcome after STEMI; moderate and severe hyperglycaemia, and also hypoglycaemia, are associated with increased 30-day mortality, irrespective of history of diabetes.³⁵ Due to the small number of hypoglycaemic patients in our study, we were not able to verify a U-shaped relationship between admission glycaemia and adverse outcome after ACS.

In conclusion, the data from this study have shown that hyperglycaemia at admission is associated with a worse outcome for all patients admitted with ACS. Complications in general, cardiogenic shock, cerebrovascular insult and in-hospital mortality increased with higher levels of blood glucose. An elevated glucose level in ACS patients on admission remained a significant independent predictor of in-hospital mortality after adjustment for multiple risk factors known to be associated with increased in-hospital mortality. The impact of a higher admission glucose level on in-hospital mortality was even more important for non-diabetic than for diabetic ACS patients. Thus, non-diabetic patients with hyperglycaemia at admission were at special risk. They may need particular attention at hospital admission, therefore more aggressive screening strategies should be applied to all ACS patients in order to recognise these high-risk patients. According to our results, hyperglycaemia on admission clearly predicts a worse outcome and could therefore be used as an early marker of high-risk individuals. These patients may benefit from an appropriate treatment strategy, including strict glycaemic control. Further studies to evaluate the effect of acute and intensive glycaemic control on reducing in-hospital mortality in patients admitted for ACS are needed.

Acknowledgements

For the years 2005/2006, the AMIS Plus Registry was funded by grants from (in alphabetical order): AstraZeneca, Biotronik, Essex Chemie, Guidant AG, Johnson & Johnson, Medtronic AG, A Menarini AG, Merck Sharp Dohme Chibret, Pfizer AG, Rahn Foundation, Sanofi, SPSS AG, St Jude Medical and Takeda (all in Switzerland). This support is acknowledged. The supporting institutions did not play any role in the design of the registry, data collection, analysis or interpretation.

Conflicts of interest statement

None declared.

References

- Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. *JAMA* 1979;**241**:2035-8.
- Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 1993;**16**:434-44.
- Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. *Diabetes Care* 1999;**22**:233-40.
- Jacoby RM, Nesto RW. Acute myocardial infarction in the diabetic patient: pathophysiology, clinical course and prognosis. *J Am Coll Cardiol* 1992;**20**:736-44.
- Abbud ZA, Shindler DM, Wilson AC, Kostis JB. Effect of diabetes mellitus on short- and long-term mortality rates of patients with acute myocardial infarction: a statewide study. Myocardial Infarction Data Acquisition System Study Group. *Am Heart J* 1995;**130**(1):51-8.
- Aronson D, Rayfield EJ, Chesebro JH. Mechanisms determining course and outcome of diabetic patients who have had acute myocardial infarction. *Ann Intern Med* 1997;**126**:296-306.
- Stranders I, Diamant M, van Gelder RE *et al*. Admission blood glucose level as risk indicator of death after myocardial infarction in patients with and without diabetes mellitus. *Arch Intern Med* 2004;**164**:982-8.
- McGuire DK, Emanuelsson H, Granger CB *et al*. Influence of diabetes mellitus on clinical outcomes across the spectrum of acute coronary syndromes. Findings from the GUSTO-IIb study. GUSTO IIb Investigators. *Eur Heart J* 2000;**21**:1750-8.
- Ainla T, Baburin A, Teesalu R, Rahu M. The association between hyperglycaemia on admission and 180-day mortality in acute myocardial infarction patients with and without diabetes. *Diabet Med* 2005;**22**:1321-5.
- Bolk J, van der Ploeg T, Cornel JH, Arnold AE, Sepers J, Umans VA. Impaired glucose metabolism predicts mortality after a myocardial infarction. *Int J Cardiol* 2001;**79**:207-14.
- Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *Lancet* 2000;**355**:773-8.
- Foo K, Cooper J, Deane A *et al*. A single serum glucose measurement predicts adverse outcomes across the whole range of acute coronary syndromes. *Heart* 2003;**89**:512-16.
- Goyal A, Mahaffey KW, Garg J *et al*. Prognostic significance of the change in glucose level in the first 24 h after acute myocardial infarction: results from the CARDINAL study. *Eur Heart J* 2006;**27**:1289-97.
- Malmberg K, Norhammar A, Wedel H, Ryden L. Glycometabolic state at admission: important risk marker of mortality in conventionally treated patients with diabetes mellitus and acute myocardial infarction: long-term results from the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study. *Circulation* 1999;**99**:2626-32.
- Malmberg K, Ryden L, Hamsten A, Herlitz J, Waldenstrom A, Wedel H. Mortality prediction in diabetic patients with myocardial infarction: experiences from the DIGAMI study. *Cardiovasc Res* 1997;**34**:248-53.
- Norhammar AM, Ryden L, Malmberg K. Admission plasma glucose. Independent risk factor for long-term prognosis after myocardial infarction even in nondiabetic patients. *Diabetes Care* 1999;**22**:1827-31.
- Straumann E, Kurz DJ, Muntwyler J *et al*. Admission glucose concentrations independently predict early and late mortality in patients with acute myocardial infarction treated by primary or rescue percutaneous coronary intervention. *Am Heart J* 2005;**150**:1000-06.
- Svensson AM, McGuire DK, Abrahamsson P, Dellborg M. Association between hyper- and hypoglycaemia and 2-year all-cause mortality risk in diabetic patients with acute coronary events. *Eur Heart J* 2005;**26**:1255-61.
- Wahab NN, Cowden EA, Pearce NJ, Gardner MJ, Merry H, Cox JL. Is blood glucose an independent predictor of mortality in acute myocardial infarction in the thrombolytic era? *J Am Coll Cardiol* 2002;**40**:1748-54.
- Fassa AA, Urban P, Radovanovic D *et al*. Trends in reperfusion therapy of ST segment elevation myocardial infarction in Switzerland: six year results from a nationwide registry. *Heart* 2005;**91**:882-8.
- Urban P, Bernstein M, Costanza M, Simon R, Frey R, Erne P for the AMIS Investigators. An Internet-based registry of acute myocardial infarction in Switzerland. *Kardiovaskuläre Medizin* 2000;**3**:430-40.
- Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;**40**:373-83.
- Tenerz A, Lonnberg I, Berne C, Nilsson G, Leppert J. Myocardial infarction and prevalence of diabetes mellitus. Is increased casual blood glucose at admission a reliable criterion for the diagnosis of diabetes? *Eur Heart J* 2001;**22**:1102-10.
- Norhammar A, Tenerz A, Nilsson G *et al*. Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. *Lancet* 2002;**359**:2140-4.
- Timmer JR, van der Horst IC, Ottervanger JP *et al*. Prognostic value of admission glucose in non-diabetic patients with myocardial infarction. *Am Heart J* 2004;**148**:399-404.
- Andersen HR, Nielsen TT, Rasmussen K *et al*. A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. *N Engl J Med* 2003;**349**:733-42.
- Keeley EC, Cigarroa JE. Facilitated primary percutaneous transluminal coronary angioplasty for acute ST segment elevation myocardial infarction: rationale for reuniting pharmacologic and mechanical revascularization strategies. *Cardiol Rev* 2003;**11**:13-20.
- Widimsky P, Groch L, Zelizko M, Aschermann M, Bednar F, Suryapranata H. Multicentre randomized trial comparing transport to primary angioplasty vs immediate thrombolysis vs combined strategy for patients with acute myocardial infarction presenting to a community hospital without a catheterization laboratory. The PRAGUE study. *Eur Heart J* 2000;**21**:823-31.
- Malmberg K, Ryden L, Efendic S *et al*. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. *J Am Coll Cardiol* 1995;**26**:57-65.
- Malmberg K, Ryden L, Wedel H *et al*. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. *Eur Heart J* 2005;**26**:650-61.
- Morrow DA, Antman EM, Charlesworth A *et al*. TIMI risk score for ST-elevation myocardial infarction: A convenient, bedside, clinical score for risk assessment at presentation: An intravenous nPA for treatment of infarcting myocardium early II trial substudy. *Circulation* 2000;**102**:2031-7.
- Sabatine MS, Antman EM. The thrombolysis in myocardial infarction risk score in unstable angina/non-ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 2003;**41**(4 Suppl S):89S-95S.
- Ryden L, Standl E, Bartnik M *et al*. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). *Eur Heart J* 2007;**28**:88-136.
- Erne P, Radovanovic D, Urban P, Stauffer J-C, Bertel O, Gutzwiller F for the AMIS Plus Investigators. Early drug therapy and in-hospital mortality following acute myocardial infarction. *Heart Drug* 2003;**3**:134-40.
- Pinto DS, Skolnick AH, Kirtane AJ *et al*. U-shaped relationship of blood glucose with adverse outcomes among patients with ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 2005;**46**:178-80.