Short-term mortality of myocardial infarction patients with diabetes or hyperglycaemia during admission

J Sala, R Masiá, F-J González de Molina, J M Fernández-Real, M Gil, D Bosch, W Ricart, M Senti, J Marrugat, for the REGICOR Investigators

Aim: The hypothesis that patients with hyperglycaemia during admission, regardless of previous diagnosis of diabetes, have worse prognosis than those with normal glucose values is controversial. The objective was to assess the role of hyperglycaemia on short-term mortality after myocardial infarction (MI).

Methods and Results: A cohort study nested in a prospective registry of MI patients in the reference hospital of Gerona, Spain was performed. All consecutive MI patients under 75 were registered between 1993 and 1996. Patient and clinical characteristics, including previous diagnosis of diabetes, glycaemia on admission and in the next four days, were recorded. Patients with glycaemia on admission or four day mean glycaemia >6.67 mmol/l were considered hyperglycaemic. The main outcome measure was mortality at 28 days. Of 662 patients with MI included, 195 (29.7%) had previously known diabetes mellitus, but 457 (69.0%) had glycaemia >6.67 mmol/l on admission. Patients with hyperglycaemia on admission were older, more often female, more frequently had a previous diagnosis of diabetes, developed more complications, and had higher 28 day mortality. The effect of admission glycaemia >6.67 mmol/l on 28 day mortality was independent of major confounding factors, particularly previous diagnosis of diabetes (OR=4.20, 95% confidence intervals 1.18 to 14.96).

Conclusions: Higher 28 day mortality was observed among MI patients with glycaemia on admission >6.67 mmol/l compared with patients with lower levels, independently of major confounding variables and, particularly, previous diagnosis of diabetes. This early, simple, and inexpensive marker of bad prognosis after MI should prompt the application of more aggressive treatment of MI and risk factors and, probably, of glycaemia during admission.

Coronary heart disease is the main cause of death in diabetic patients’ and patients with myocardial infarction (MI) previously diagnosed of diabetes have worse short-term prognosis than non-diabetic patients. Although some authors have found a correlation between blood glucose on admission and severity of acute MI, there is no agreement on whether patients with hyperglycaemia on and during admission, regardless of previous diagnosis of diabetes, have worse prognosis than those with normal glucose concentrations.

Hospital MI registries include good assessment of severity and comorbidity. In particular, the REGICOR (Registre Gironí del Cor) study—an ongoing prospective registry of consecutive, diabetic, and non-diabetic MI patients in the only reference hospital in Girona, Spain—provides an appropriate setting for assessing the above issue.

The aim of this study was to assess whether hyperglycaemia on or during admission was associated with worse 28 day mortality in patients with MI.

METHODS

Patients

Patients analysed were recruited between 1993 and 1996 for this cohort study. All consecutive MI patients 74 years old or younger who attended the emergency room within 48 hours after onset of symptoms and who survived long enough to have a glycaemia determined on admission were included. Residence outside the study area was considered an exclusion criterion.

MI, diabetes mellitus, and end point definition

MI was diagnosed based on an adaptation of WHO-MONICA project methods, which take into account the type of symptoms, electrocardiographic (ECG) findings, cardiac enzyme values, and history of ischaemic heart disease and necropsy interpretation in fatal cases. Diagnosis of Q wave MI was based on the presence of a definite electrocardiogram (new Q or QS waves) and at least one of the following two findings: increased MI enzymes (twofold or greater increase beyond upper normal value), and typical pain (located in the anterior chest wall and lasting 20 minutes or more for which no cause other than ischaemic heart disease was found). Non-Q wave MI diagnosis was based on serial electrocardiograms with only ST segment and/or T wave changes in patients with cardiac enzyme activities at least twice the normal limit, together with typical chest pain lasting more than 20 minutes. An event in the same patient was considered a new episode when more than 28 days had elapsed after a preceding event. The study hospital applies written MI management routines in accordance with international guidelines. All patients (or their relatives when necessary) were asked about previous diagnosis of diabetes and any related treatment.

Sample size

Sample size was calculated to provide a statistical power of 0.80 in a two tailed test with an α risk of 0.05 if a difference greater than or equal to eight percentage units in the 28 day mortality was observed between hyperglycaemic patients and the rest (the hypothesis was 15% and 6%, respectively). With these conditions, 301 patients were required for each group. This sample size permits detection of adjusted relative
risks for hyperglycaemia greater than or equal to 2.1 as statistically significant (p<0.05). Primary end point was 28 day mortality.

**Study variables measured in the acute phase of MI**

The following variables were recorded: demographics, history of hypertension, diabetes mellitus with a questionnaire that included questions on previous diagnosis by a physician and treatment for diabetes, MI location, presence of Q waves on electrocardiogram, development of acute pulmonary oedema or cardiogenic shock, presence of severe arrhythmia (defined as the occurrence of at least one episode of ventricular fibrillation or sustained ventricular tachycardia requiring immediate medical intervention during the acute phase of myocardial infarction within 72 hours of myocardial infarction onset).

### Table 1

Characteristics of myocardial infarction patients by admission glycaemia levels in the REGICOR study (Gerona, Spain, 1993–96)

<table>
<thead>
<tr>
<th>Glycaemia on admission</th>
<th>&lt;6.67 mmol/l</th>
<th>p Value</th>
<th>&gt;6.67 mmol/l</th>
<th>p Value</th>
<th>Four day mean glycaemia</th>
<th>&lt;6.67 mmol/l</th>
<th>p Value</th>
<th>&gt;6.67 mmol/l</th>
<th>p Value</th>
<th>Without previous diagnosis of diabetes</th>
<th>p Value</th>
<th>Previous diagnosis of diabetes</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>205</td>
<td>457</td>
<td>242</td>
<td>362</td>
<td>445</td>
<td>195</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>57.7 (11.4)</td>
<td>62.7 (9.4)</td>
<td>&lt;0.001</td>
<td>12.4</td>
<td>23.5</td>
<td>&lt;0.001</td>
<td>64.3 (8.4)</td>
<td>60.1 (10.7)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women [%]</td>
<td>9.3</td>
<td>22.8</td>
<td>&lt;0.001</td>
<td>43.4</td>
<td>46.6</td>
<td>NS</td>
<td>42.4</td>
<td>53.9</td>
<td>0.007</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>52.2</td>
<td>41.9</td>
<td>0.013</td>
<td>51.3</td>
<td>40.7</td>
<td>0.011</td>
<td>30.7</td>
<td>51.4</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>8.2</td>
<td>40.3</td>
<td>&lt;0.001</td>
<td>8.5</td>
<td>45.1</td>
<td>&lt;0.001</td>
<td>47.1</td>
<td>56.7</td>
<td>0.025</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>54.4</td>
<td>47.7</td>
<td>0.111</td>
<td>50.8</td>
<td>47.1</td>
<td>NS</td>
<td>47.1</td>
<td>56.7</td>
<td>0.025</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>History of angina</td>
<td>6.9</td>
<td>12.3</td>
<td>0.035</td>
<td>7.9</td>
<td>12.8</td>
<td>0.061</td>
<td>8.6</td>
<td>16.5</td>
<td>0.003</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of heart failure</td>
<td>1.9</td>
<td>2.9</td>
<td>NS</td>
<td>1.7</td>
<td>3.6</td>
<td>NS</td>
<td>1.5</td>
<td>3.1</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>1.9</td>
<td>2.9</td>
<td>NS</td>
<td>1.7</td>
<td>3.6</td>
<td>NS</td>
<td>1.5</td>
<td>3.1</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Arrhythmias‡</td>
<td>15.1</td>
<td>25.1</td>
<td>0.005</td>
<td>17.6</td>
<td>24.4</td>
<td>0.049</td>
<td>21.2</td>
<td>24.5</td>
<td>NS</td>
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<tr>
<td>Anterior myocardial infarction</td>
<td>32.8</td>
<td>35.0</td>
<td>NS</td>
<td>30.8</td>
<td>35.4</td>
<td>NS</td>
<td>34.7</td>
<td>33.9</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Q wave myocardial infarction</td>
<td>18.7</td>
<td>18.1</td>
<td>NS</td>
<td>18.8</td>
<td>17.8</td>
<td>NS</td>
<td>17.4</td>
<td>21.1</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Angina post myocardial infarction</td>
<td>25.9</td>
<td>25.0</td>
<td>NS</td>
<td>22.2</td>
<td>28.1</td>
<td>0.123</td>
<td>24.4</td>
<td>27.9</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28 day re-infarction</td>
<td>2.7</td>
<td>2.7</td>
<td>NS</td>
<td>2.8</td>
<td>2.5</td>
<td>NS</td>
<td>1.5</td>
<td>5.6</td>
<td>0.006</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28 day APE or cardiogenic shock</td>
<td>4.9</td>
<td>18.4</td>
<td>&lt;0.001</td>
<td>4.6</td>
<td>20.2</td>
<td>&lt;0.001</td>
<td>8.8</td>
<td>25.1</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28 day mortality</td>
<td>1.5</td>
<td>10.3</td>
<td>&lt;0.001</td>
<td>1.7</td>
<td>9.1</td>
<td>&lt;0.001</td>
<td>5.4</td>
<td>12.3</td>
<td>0.002</td>
<td></td>
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<tr>
<td>Thrombolysis</td>
<td>34.0</td>
<td>38.3</td>
<td>NS</td>
<td>40.4</td>
<td>37.0</td>
<td>NS</td>
<td>41.6</td>
<td>27.3</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplatelet drugs</td>
<td>98.0</td>
<td>96.5</td>
<td>NS</td>
<td>98.8</td>
<td>97.0</td>
<td>0.154</td>
<td>97.5</td>
<td>96.4</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28 day coronary angiograms</td>
<td>19.5</td>
<td>17.4</td>
<td>NS</td>
<td>17.5</td>
<td>18.3</td>
<td>NS</td>
<td>17.0</td>
<td>20.8</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n, Number of patients; NS, non-statistically significant; APE, acute pulmonary oedema. *Mean (SD); †κ=0.24. ‡Occurrence of ventricular fibrillation or sustained ventricular tachycardia requiring immediate medical intervention during the acute phase of myocardial infarction within 72 hours of myocardial infarction onset.

### Table 2

Characteristics of 28 day deceased and survivors after an acute myocardial infarction in the REGICOR Study (Gerona, Spain, 1993–96)

<table>
<thead>
<tr>
<th>Deceased</th>
<th>Survivors</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=50</td>
<td>n=612</td>
<td></td>
</tr>
<tr>
<td>Age*</td>
<td>63.1 (10.4)</td>
<td>61.0 (10.3)</td>
</tr>
<tr>
<td>Women [%]</td>
<td>28.0%</td>
<td>17.8%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>44.9%</td>
<td>46.4%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>50.0%</td>
<td>28.9%</td>
</tr>
<tr>
<td>Smoking</td>
<td>29.2%</td>
<td>46.4%</td>
</tr>
<tr>
<td>Glycaemia &gt;6.67 mmol/l on admission</td>
<td>94.0%</td>
<td>67.0%</td>
</tr>
<tr>
<td>Four day mean glycaemia &gt;6.67 mmol/l</td>
<td>89.2%</td>
<td>58.0%</td>
</tr>
<tr>
<td>History of angina</td>
<td>60.0%</td>
<td>48.9%</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>4.0%</td>
<td>2.5%</td>
</tr>
<tr>
<td>History of heart failure</td>
<td>28.0%</td>
<td>9.2%</td>
</tr>
<tr>
<td>Post myocardial infarction angina</td>
<td>17.4%</td>
<td>26.0%</td>
</tr>
<tr>
<td>Arrhythmias†</td>
<td>52.1%</td>
<td>19.6%</td>
</tr>
<tr>
<td>Anterior myocardial infarction</td>
<td>59.5%</td>
<td>32.5%</td>
</tr>
<tr>
<td>Non-Q wave myocardial infarction</td>
<td>16.7%</td>
<td>18.4%</td>
</tr>
<tr>
<td>APE or cardiogenic shock</td>
<td>71.4%</td>
<td>9.7%</td>
</tr>
<tr>
<td>28 day re-infarction</td>
<td>4.2%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Therapeutic and diagnostic procedures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>14.0%</td>
<td>38.9%</td>
</tr>
<tr>
<td>Antiplatelet drugs</td>
<td>86.0%</td>
<td>97.9%</td>
</tr>
<tr>
<td>28 day coronary angiograms</td>
<td>8.2%</td>
<td>18.8%</td>
</tr>
</tbody>
</table>

n, Number of patients; NS, non-statistically significant; APE, acute pulmonary oedema. *Mean (SD). †Occurrence of ventricular fibrillation or sustained ventricular tachycardia requiring immediate medical intervention during the acute phase of myocardial infarction within 72 hours of myocardial infarction onset.
were assessed with the differences between hyperglycaemic patients and the rest was calculated and used as a predictor of mortality. Determinations existed after that made on admission, a mean glycaemia to obtain a sensitivity higher than 90%, to establish the optimum cut off value for admission and mean of the subsequent glycaemias was high ($\kappa=0.65$); correlation coefficient was 0.88 ($p<0.001$). However, concordances of admission glycaemia $>6.67$ mmol/l with previous diagnosis of diabetes ($\kappa=0.25$) and with mean four day glycaemia $>6.67$ mmol/l ($\kappa=0.41$) were low. Thrombolysis, antiplatelet drugs, and coronary angiography were similarly used in all types of patients. The effect of hyperglycaemia in patients with and without history of diabetes was similar: patients with glycaemias $>6.67$ mmol/l had worse outcome in both groups (table 1).

**Variables associated with hyperglycaemia on admission ($>6.67$ mmol/l)** Compared with the rest, patients with hyperglycaemia on admission were older, were more often female, more frequently had a previous diagnosis of diabetes, and developed acute pulmonary oedema or cardiogenic shock and severe ventricular arrhythmias. Mortality at 28 days was significantly higher in patients with hyperglycaemia on admission (table 1). Kaplan-Meier survival curves showed a large difference in survival between patients with and without hyperglycaemia on admission (fig 1), between patients with and without mean four day hyperglycaemia (fig 2), between patients with and without previous diagnosis of diabetes (table 2).

In 604 patients with more than two measurements within the four days after onset of symptoms, concordance between glycaemia on admission and mean of the subsequent glycaemias was high ($\kappa=0.65$); correlation coefficient was 0.88 ($p<0.001$). However, concordances of admission glycaemia $>6.67$ mmol/l with previous diagnosis of diabetes ($\kappa=0.25$) and with mean four day glycaemia $>6.67$ mmol/l ($\kappa=0.41$) were low. Thrombolysis, antiplatelet drugs, and coronary angiography were similarly used in all types of patients. The effect of hyperglycaemia in patients with and without history of diabetes was similar: patients with glycaemias $>6.67$ mmol/l had worse outcome in both groups (table 1).

**Variables associated with mortality** Compared with deceased patients, 28 day survivors were younger, less frequently had a previous diagnosis of diabetes and heart failure and less often presented severe ventricular arrhythmias, anterior MI, acute pulmonary oedema, or cardiogenic shock. However, a greater proportion of non-Q wave MI was observed. Thrombolysis, antiplatelet drugs, and coronary angiography were more often used in survivors (table 2).

Glycaemia $>6.67$ mmol/l was associated with higher mortality in patients who were not previously diagnosed of diabetes (8.5% versus 1.1%, $p<0.001$). Although in patients with previous diagnosis of diabetes the difference in 28 day mortality was high (6.3% versus 12.8%) it did not reach statistical significance. However, only one of 16 patients previously diagnosed with diabetes with admission glycaemia $>6.67$ mmol/l died within 28 days (fig 3).
Acute hyperglycaemia has been found to induce oxidative toxic effects of high blood glucose levels on cell function. Hence, independently of the cause of hyperglycaemia, there is evidence for multiple deleterious effects of acute hyperglycaemia such as vasoconstriction through NO decrease, activation of coagulation, and increased expression of adhesion molecules.

Increased glucose levels can also increase protein conjugation, a process by which glucose is covalently bound to protein molecules.

The white blood cells' ability to phagocytose is also reduced. Acute hyperglycaemia causes a down-regulation of the expression of adhesion molecules. This results in decreased cell-to-cell adhesion, which can impair the ability of immune cells to effectively combat infections.

Several mechanisms may explain the role of hyperglycaemia in the acute phase of MI and trigger a non-specific stress reaction leading to an impaired plasma insulin response resulting in hyperglycaemia. Independently of the cause of hyperglycaemia, there is evidence for toxic effects of high blood glucose levels on cell function. Acute hyperglycaemia has been found to induce oxidative stress, probably via generation of free radicals. This may occur by auto-oxidation of glucose, labile glycation, or intracellular activation of the polyol pathway. The free radicals may then mediate some of the effects associated with hyperglycaemia such as vasoconstriction through NO decrease, activation of coagulation, and increased expression of adhesion molecules. Increased glucose levels can also increase protein conjugation.
kinase C activity. This is an immediate effect of hyperglycaemia, although there is evidence to suggest that the effect of hyperglycaemia may persist for some time after blood glucose levels return to normal. Various cellular changes associated with this acute hyperglycaemia are probably mediated via protein kinase C activity, for example, increased endothelin secretion, increased collagen IV and fibronectin secretion and also increased expression of adhesion molecules on the vascular endothelium involved in macrophage migration.

Other than cellular toxicity, it has been shown that hyperglycaemia has deleterious effects on endothelium dependent vasodilatation, worsening myocardial ischaemia, and that treatment with insulin attenuates these effects. Furthermore, basal fibrinolytic activity is diminished in diabetics and the excess of insulin present in diabetes type II patients increases plasminogen activator inhibitor 1 (PAI 1), also causing a decrease of fibrinolytic activity. Thus, an accentuation of ischaemia and an increase of thrombogenicity contribute to a greater severity of MI in hyperglycaemic patients.

Study characteristics and clinical implications
Non-fasting sampling could be claimed to have been responsible for some glycaemics over 6.67 mmol/l on admission. However, successive determinations were obtained after eight hour fasting and yielded results similar to those obtained with admission blood sample, as shown by the excellent concordance found between them. The number of subsequent determinations decreased as some patients died early after admission. This contributed to decreasing somewhat the intensity of the association between four day mean fasting glycaemia and mortality in 24 hour survivors.

All factors that may confound the relation between glycaemia levels and 28 day case fatality (that is, severity, comorbidity, age, sex and, particularly, previous diagnosis of diabetes) were adjusted for in a logistic model. Therefore, admission glucose concentration is a powerful predictor of early mortality after MI, regardless of any other consideration. Glycosylated haemoglobin was not determined, which constitutes a limitation of the study.

This study shows that many patients who met diabetes criteria according to their admission and four day glycaemia measurements during admission had not been previously diagnosed. It should be emphasised that these were consecutive patients of a general population, including diabetics and non-diabetics. Furthermore, hyperglycaemia on admission was associated with higher 28 day mortality independently of previous diagnosis of diabetes and was a stronger predictor of outcome. This suggests that management of hyperglycaemia during the acute phase of MI could be a major issue requiring further investigation and could be important for future therapeutic approaches. In fact, only the DIGAMI MI trial showed the benefit of treating diabetic patients with pump insulin infusion. In this Scandinavian trial, one year mortality was significantly reduced by 25% in MI patients assigned to aggressive plasma insulin lowering treatment compared with those who were not. However, it is not clear that this intervention reduced mortality in non-diabetic patients. Diabetes Care 1999;22:1527–31.

Our data support the idea that the higher 28 day mortality exists among MI patients younger than 75 years with admission glycaemia >6.67 mmol/l compared with patients with lower levels, independently of major confounding variables, particularly previous diagnosis of diabetes. Whether this is only an epiphenomenon or an effect of glucose toxicity that worsens myocardial injury remains to be elucidated.

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Conflicts of interest: none.

REFERENCES


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