Mortality prediction in diabetic patients with myocardial infarction: experiences from the DIGAMI study

Klas Malmberg a,*, Lars Rydén a, Anders Hamsten b, Johan Herlitz c, Anders Waldenström d, Hans Wedel e,1

a Departments of Cardiology, Karolinska Hospital, S-171 76 Stockholm, Sweden
b Department of Medicine, Karolinska Hospital, Stockholm, Sweden
c Department of Medicine, Sahlgrenska Hospital, Göteborg, Sweden
d Department of Medicine, Norrland University Hospital, Umeå, Sweden
e Nordic School for Public Health, Göteborg, Sweden

Received 11 July 1996; accepted 2 December 1996

Abstract

Objectives: We analysed predictors of 1-year mortality following acute myocardial infarction in patients with diabetes mellitus by applying uni- and multivariate statistics on the DIGAMI cohort. Background: Diabetic patients with acute myocardial infarction have a poor prognosis. This may depend on a poor metabolic control, a hypothesis that was tested in DIGAMI, a prospective randomised study. In this trial institution of immediate intensive insulin treatment reduced 1-year mortality by 30%. Methods: We recruited 620 diabetic patients with acute myocardial infarction, 314 of whom served as controls, while the remaining 306 patients were treated with an acute insulin–glucose infusion followed by multidose subcutaneous insulin. Results: Age, previous myocardial damage, duration of the diabetes and previous insulin therapy were significantly related to 1-year mortality, while conventional risk factors lacked independent prognostic weight. Female sex was not linked to mortality when controlling for the confounding effects of other predictors. One of the strongest predictors of a fatal outcome, in particular during the hospital phase, was blood glucose at hospital admission. Beta-blockade appeared to exert a striking, independent secondary-preventive effect. Conclusions: It seems that good metabolic control and not conventional risk factors is of major importance for diabetic patients sustaining acute myocardial infarction. Also treatment with beta-blockade seems to be of special importance in this category of patients.

Keywords: Myocardial infarction; Diabetes; Mortality; Morbidity; Prediction; Beta-blockers; Insulin; Human

1. Introduction

The short- and long-term prognosis of diabetic patients sustaining acute myocardial infarction has since long been known to be poor. In this respect, female patients have been considered at particular risk [1]. Besides an increased acute mortality [2–5], diabetic subjects have a high likelihood of suffering reinfarctions, of which many are fatal [2,6,7]. Many factors may contribute to this unfavourable outcome, such as severe and diffuse coronary artery disease, diabetic cardiomyopathy, disturbed autonomic tone and abnormal fibrinolytic and platelet functions along with purely metabolic factors causing more oxygen-consuming substrate utilisation during acute myocardial ischaemia [8].

The recent DIGAMI study demonstrated that the 1-year prognosis in diabetic patients with acute myocardial infarc-
dial infarction by applying uni- and multivariate statistics on the DIGAMI cohort. Besides shedding light on the mechanisms behind the beneficial effects of improving insulin–glucose homeostasis new hypotheses are generated to be examined in future studies of diabetic patients with myocardial infarction.

2. Methods

2.1. Study design

A detailed description of DIGAMI including study design, definitions and methods has been given elsewhere [9,10]. Briefly, this is a multicentre, randomised, prospective study on the effect on mortality and morbidity of an intravenous infusion of insulin–glucose followed by 4-dose subcutaneous insulin therapy given to patients with suspected acute myocardial infarction within the preceding 24 h and diabetes mellitus. The infusion was initiated as soon as possible after the onset of symptoms and continued for at least 24 h or until stable normoglycaemia. All patients were followed prospectively with scheduled visits at 3 and 12 months after randomisation. Prior to randomisation the patients were stratified into one of 4 groups according to a risk classification and previous insulin treatment.

Patients randomised to insulin treatment (infusion group) received an insulin–glucose infusion followed by multi-dose subcutaneous insulin treatment for at least 3 months while those who were assigned to the control group received conventional treatment. The subcutaneous insulin treatment was instituted immediately after the cessation of the infusion. Concurrent medication was managed according to strict, predefined guidelines to achieve a uniform treatment in the two groups, apart from the use of insulin. If there were no contraindications, thrombolysis, beta-blocker and aspirin treatments were initiated as soon as possible. All patients were followed prospectively for 1 year with scheduled visits at 3 and 12 months after randomisation when specific case record forms were completed. These included information on mortality and morbidity. No patient was lost to follow-up.

2.2. Patient material

Altogether 1240 diabetic patients with suspected acute myocardial infarction were admitted to the 19 participating CCUs during the recruitment period between January 1990

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control group (n = 514)</th>
<th>Infusion group (n = 306)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68 ± 9</td>
<td>67 ± 9</td>
<td>n.s.</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>197 63</td>
<td>191 62</td>
<td>n.s.</td>
</tr>
<tr>
<td>Female</td>
<td>117 37</td>
<td>115 38</td>
<td>n.s.</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27 ± 4</td>
<td>27 ± 4</td>
<td>n.s.</td>
</tr>
<tr>
<td>Previous diseases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>117 37</td>
<td>121 40</td>
<td>n.s.</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>164 52</td>
<td>176 58</td>
<td>n.s.</td>
</tr>
<tr>
<td>Hypertension</td>
<td>154 49</td>
<td>143 47</td>
<td>n.s.</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>70 22</td>
<td>69 23</td>
<td>n.s.</td>
</tr>
<tr>
<td>Type of diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-insulin-dependent</td>
<td>265 84</td>
<td>251 82</td>
<td>n.s.</td>
</tr>
<tr>
<td>Insulin-dependent</td>
<td>49 16</td>
<td>55 18</td>
<td>n.s.</td>
</tr>
<tr>
<td>Previously unknown</td>
<td>47 15</td>
<td>31 10</td>
<td>n.s.</td>
</tr>
<tr>
<td>Duration (years)</td>
<td>10 ± 10</td>
<td>10 ± 10</td>
<td>n.s.</td>
</tr>
<tr>
<td>Anti-diabetic treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>47 15</td>
<td>31 10</td>
<td>n.s.</td>
</tr>
<tr>
<td>Diet</td>
<td>39 12</td>
<td>33 11</td>
<td>n.s.</td>
</tr>
<tr>
<td>Tablets</td>
<td>115 37</td>
<td>140 46</td>
<td>n.s.</td>
</tr>
<tr>
<td>Insulin</td>
<td>113 36</td>
<td>102 33</td>
<td>n.s.</td>
</tr>
<tr>
<td>Blood glucose at randomisation (mmol/l)</td>
<td>15.7 ± 4.2</td>
<td>15.4 ± 4.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>HbA1c at randomisation (%)</td>
<td>8.0 ± 2.0</td>
<td>8.2 ± 1.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>Blood glucose 24 h after randomisation (mmol/l)</td>
<td>11.7 ± 4.1</td>
<td>9.6 ± 3.3</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Blood glucose at hospital discharge (mmol/l)</td>
<td>9.0 ± 5.0</td>
<td>8.2 ± 3.1</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Values are number and percentage of patients in each group or mean ± s.d.
and December 1993. Half of them were excluded, leaving 620 patients for randomisation. A detailed report of exclusion criteria and characteristics of excluded patients has been given elsewhere [10]. Of the 620 study patients, 314 were allocated to the control group and 306 to the infusion group. Baseline characteristics demonstrated that the two groups were well balanced at the time of randomisation (Table 1).

There were 232 female (38%) and 388 male (62%) patients. The female patient group was older than the male (70 ± 9 vs 66 ± 9 years; \( P < 0.001 \)) and had fewer previous infarctions (28 vs 44%; \( P < 0.001 \)). Hypertension was more prevalent among women than men (56 vs 44%; \( P < 0.01 \)) and the duration of diabetes was longer in the female group (11 ± 11 vs 9 ± 9 years; \( P < 0.05 \)). With these exceptions there were no sex differences regarding baseline characteristics.

### 2.3. Statistics

Standard statistical methods were used. The significance of the differences between the two groups has been tested by Student’s \( t \)-test and Fisher’s exact test.

The proportional hazards regression model (Cox model) was used to evaluate the relationship between risk factors and mortality [12]. First an univariate model estimated relative risks (RR) and their confidence intervals from the relative hazards. To find variables which contributed independently to mortality, significant variables from the univariate model together with sex, were analysed in a stepwise multivariate Cox model. SAS statistical package version 6.08 was used and a two-tailed \( P \)-value of less than 0.05 was considered statistically significant.

### 3. Results

#### 3.1. Treatment

At hospital discharge 87% of the patients in the infusion group were on insulin treatment compared with 43% in the control group (\( P < 0.0001 \)). The corresponding proportions were 80 and 45% (\( P < 0.0001 \)) after 3 months and 72 and 49% after 1 year (\( P < 0.0001 \)), respectively. Apart from the administration of insulin, the two groups did not differ as regards treatment with beta-blockers, aspirin, ACE-inhibitors and nitrates during the year of follow-up.

At randomization the two groups did not differ in glycated haemoglobin (HbA1c; Table 1). HbA1c decreased significantly in both groups during follow-up. The reduction was more prominent in the infusion group both at 3 (1.1 ± 1.6 vs 0.4 ± 1.5%; \( P < 0.0001 \)) and 12 months (0.9 ± 1.9 vs 0.4 ± 1.8%; \( P < 0.01 \)). Fasting blood glucose 1 year after randomisation did not differ between the two groups.

#### 3.2. Mortality

After 1 year 82 (26%) deaths had occurred in the control group compared to 58 (19%) in the infusion group (relative mortality reduction 30%; \( P = 0.027 \)). Most of the mortality reduction was obtained after discharge from hospital. Among patients without prior insulin treatment and with low cardiovascular risk (\( n = 272 \)), mortality was significantly reduced already during the hospital phase, and after 1 year there were 24 (18.0%) deaths in the control group and 12 (8.6%) in the infusion group (relative mortality reduction 52%; \( P = 0.020 \)). The overall 1-year mortality tended to be higher among females than males (26.3 vs 20.4%; \( P = 0.092 \)).

Most patients died from congestive heart failure (66%). There was a trend towards less cardiovascular deaths of all kinds in the insulin treated group which did not reach the level of statistical significance. A detailed analysis of causes of death has been reported elsewhere [11].

#### 3.3. Univariate prediction

Table 2 shows the univariate relations between cardiovascular risk factors as reported at base-line and total mortality. In the entire patient group, age, previous congestive heart failure, previous myocardial infarction, previous

**Table 2**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Univariate analyses RR (95% conf. limits 140/620)</th>
<th>P-value</th>
<th>Multivariate analyses RR (95% conf. limits 140/620)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (1 year)</td>
<td>1.07 (1.05–1.11)</td>
<td>0.0001</td>
<td>1.07 (1.04–1.10)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sex (male = 1; female = 0)</td>
<td>0.73 (0.52–1.02)</td>
<td>0.067</td>
<td>1.01 (0.69–1.47)</td>
<td>0.958</td>
</tr>
<tr>
<td>Prev. myocardial infarction</td>
<td>1.42 (1.02–1.98)</td>
<td>0.040</td>
<td>0.92 (0.61–1.41)</td>
<td>0.711</td>
</tr>
<tr>
<td>Prev. angina pectoris</td>
<td>1.52 (1.07–2.15)</td>
<td>0.018</td>
<td>1.24 (0.83–1.85)</td>
<td>0.302</td>
</tr>
<tr>
<td>Prev. cong. heart failure</td>
<td>2.57 (1.84–3.61)</td>
<td>0.0001</td>
<td>2.10 (1.37–3.21)</td>
<td>0.0007</td>
</tr>
<tr>
<td>Prev. digitalis treatment</td>
<td>1.79 (1.23–2.62)</td>
<td>0.003</td>
<td>1.05 (0.68–1.63)</td>
<td>0.824</td>
</tr>
<tr>
<td>Prev. insulin treatment</td>
<td>1.75 (1.25–2.44)</td>
<td>0.001</td>
<td>1.58 (1.05–2.39)</td>
<td>0.028</td>
</tr>
<tr>
<td>Diabetes duration (1 year)</td>
<td>1.02 (1.01–1.03)</td>
<td>0.009</td>
<td>1.015 (0.99–1.03)</td>
<td>0.081</td>
</tr>
<tr>
<td>Smokers</td>
<td>0.46 (0.28–0.77)</td>
<td>0.003</td>
<td>0.79 (0.45–1.38)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Number of deaths divided by the number of subjects at risk is presented above each column. Risk ratio (RR) with 95% confidence limits is given for one unit of risk factor.
angina pectoris, previous treatment with digitalis or insulin and the duration of diabetes mellitus were associated with mortality after 1 year. Interestingly, patients who were smokers had a significantly better 1-year prognosis than non-smokers. It is also notable that there was no mortality difference between males and females.

Table 3 gives the univariate associations between 1-year mortality and baseline gluco-metabolic state, presence of congestive heart failure and treatment during the hospital phase and at discharge. In the entire patient group the most powerful predictors for an unfavourable outcome were high blood glucose levels at admission and new-onset heart failure during hospitalisation, while thrombolytic therapy during the hospital phase and ongoing treatment with beta-blockers at hospital discharge were associated with survival. A high glycosylated haemoglobin level (HbA1c) at admission predicted increased 1-year mortality ($P < 0.05$). As expected, treatment with ACE-inhibitors did not improve survival. ACE-inhibitors were only given to patients with congestive heart failure or impaired left ventricular function, well-known markers of unfavourable long-term prognosis. We also tested the two study groups for interactions between various concomitant treatments without revealing any significant influence of this kind. However, when testing for beta-blockade, the relative risk was 0.35 (0.21–0.57) in the control group and 0.64 (0.35–1.20) in the insulin group ($P = 0.20$). This may indicate a more beneficial effect of beta-blockade among the control patients.

3.4. Multivariate analysis

Independent effects of concomitant treatment on 1-year mortality following correction for age, gender and intensive insulin intervention by multivariate Cox regression analyses are presented in Table 4. Among all patients, thrombolysis and treatment with beta-blockers at hospital discharge besides intensive insulin treatment independently reduced 1-year mortality.

Multivariate statistics were applied to evaluate the independent associations of univariate baseline predictors to 1-year mortality (Table 2). In the entire patient group age, previous congestive heart failure and previous insulin treatment turned out to be independent predictors for fatal outcome during the first year of follow-up.

Since the blood glucose level at hospital admission was a powerful predictor of mortality, attempts were made to identify clinical and biochemical parameters that related to hyperglycaemia. Elevated HbA1c ($P < 0.0001$), tachycardia ($P < 0.0001$), presence of pulmonary rales at admission ($P < 0.01$) and a high body weight ($P < 0.01$) were all independently linked to hyperglycaemia at admission in multivariate analysis.

4. Discussion

Diabetes mellitus is an independent marker of morbidity and mortality after acute myocardial infarction [2,4]. The DIGAMI study demonstrated that the unfavourable long-term prognosis was improved by insulin treatment. This therapy tended to influence favourably all cardiovascular causes of death [10,11].

An interesting finding in DIGAMI is that female sex, which has long been considered a particular risk factor, did not prove to be an independent risk when dissimilarities in baseline characteristics, most importantly age, were taken into account. The female patients were almost 4 years older than their male counterparts. The absence of multivariate analysis in previous studies may explain this discrepancy between the present and previous data. Our observation fits with data recently reported by Bueno et al. [13]. These authors proposed that the increased mortality reported for women with acute myocardial infarction relates to the impact of cardiovascular risk factors on left ventricular function rather than to sex per se. Among pre-hospital characteristics in the DIGAMI material, only age, previous heart failure and prior insulin treatment (which closely relates to the duration of diabetes) remained as independent predictors of mortality. Other risk factors identified in non-diabetic patients, such as previous myocardial infarction and hypertension, were of no importance. This is in agreement with the findings of Kuusisto et al. [14] that gluco-metabolic control and diabetes duration,
but not classical cardiovascular risk factors, predict mortality among non-insulin-dependent diabetic patients.

Metabolic control measured as fasting blood glucose or HbA1c is a major determinant of future development of coronary heart disease among patients with non-insulin-dependent diabetes mellitus [14–17]. Cardiovascular events decreased by 40% after intense treatment of insulin-dependent diabetics in the Diabetes Control and Complications Trial [18]. In the present study baseline HbA1c independently predicted the 1-year outcome. The reduction of HbA1c was most apparent in DIGAMI patients without previous insulin treatment (data not shown). This was also the group that benefited most in terms of improved 1-year mortality. Accordingly, the present data further support the notion that glycaemic control is of fundamental importance for the prevention of ischaemic complications in diabetic patients.

The institution of long-term insulin treatment in this relatively old diabetic population improved glycaemic control without harmful side-effects [11], which is in accordance with the recently published Veterans Affairs pilot study [19].

The beneficial effect of beta-blockade on survival is in agreement with subgroup analyses from earlier post-myocardial-infarction trials. These suggest that a more than 50% mortality reduction is obtained in diabetics [20–22]. It is likely that the beneficial effect has a multifactorial background. In experimental settings propranolol shifts the myocardial metabolism from free fatty acid oxidation towards glucose utilisation. This reduces myocardial oxygen consumption per mole of ATP produced and results in smaller infarcts [23]. Such effects may be of particular value in diabetics with increased levels of circulating free fatty acids [24–28]. Furthermore, beta-blockers may improve the autonomic imbalance which is present among many diabetic patients [29]. Diabetics with acute myocardial infarction have a significantly higher heart rate at hospital admission than non-diabetics [20]. This may relate to parasympathetic damage preceding a subsequent sympathetic dysfunction [29].

The mortality reduction obtained with beta-blocker treatment relates to the magnitude of heart rate reduction [30] and is most pronounced in patients with high initial heart rates [31,32]. Metoprolol, the beta-blocker used in DIGAMI, improved vagal tone and prevented ventricular fibrillation in coronary-ligated rabbits. It was postulated that the protective effect was mediated by influences on the central nervous system [33].

Mechanisms like this may be of particular relevance in diabetic patients who are more prone to sudden death than non-diabetics. In a recent report from the Honolulu Heart Program sudden death related to the degree of glucose intolerance [34]. This is of considerable interest in the perspective of the trend towards fewer sudden deaths seen among the intensively treated (insulin and beta-blockade) DIGAMI patients [11].

Although it should be interpreted with caution, beta-blockade tended to be of particular value in the control group. The result was not statistically significant, which may relate to a type II statistical error. It may be speculated that part of the beneficial mechanism of action for insulin and beta-blockade in diabetic patients with acute myocardial infarction is similar. A possible effect, common to both treatment modalities, is a reduction of free fatty acid oxidation and a concomitant promotion of glucose utilisation in the ischaemic as well as the non-ischaemic myocardium.

Hyperglycaemia at hospital admission was one of the strongest predictors of death, in particular death occurring during the hospital phase. This is in accordance with several previous studies of diabetic and non-diabetic patients [35–39]. Hyperglycaemia has been linked to extensive myocardial damage causing heart failure and secondary stress. Among the diabetics in the DIGAMI study, however, previous metabolic control (HbA1c) was the most powerful predictor of the blood glucose level at admission. Other determinants of blood glucose level were tachycardia and basal pulmonary rales, which may be related to stress. Body weight was also related to blood glucose at admission, possibly reflecting insulin resistance.

In conclusion, the mortality in diabetic patients with acute myocardial infarction is predicted by age, previous myocardial damage and the severity of the diabetic state as indicated by duration of the disease and the need for insulin treatment. In contrast, mortality is not related to conventional cardiovascular risk factors. Female sex is not an independent, unfavourable prognostic factor. Furthermore, the risk of future complications relates to the quality of glycaemic control at baseline, and it seems that institution of intensive insulin treatment considerably reduces this risk. Beta-blockers also appear to have an independent and striking secondary preventive effect in diabetics with myocardial infarction, possibly sharing some mechanisms of action with insulin.

Acknowledgements

This study was supported by grants from the Swedish Heart-Lung Foundation and Svenska Hoechst.

References


