Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus

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Abstract

Objectives: To test the hypothesis that intensive metabolic treatment with insulin-glucose infusion followed by multidose insulin treatment in patients with diabetes mellitus and acute myocardial infarction improves the prognosis.

Design: Patients with diabetes mellitus and acute myocardial infarction were randomly allocated standard treatment plus insulin-glucose infusion for at least 24 hours followed by multidose insulin treatment or standard treatment (controls).

Subjects: 620 patients were recruited, of whom 306 received intensive insulin treatment and 314 served as controls.

Main outcome measure: Long term all cause mortality.

Results: The mean (range) follow up was 3.4 (1.6-5.6) years. There were 102 (33%) deaths in the treatment group compared with 138 (44%) deaths in the control group (relative risk (95% confidence interval) 0.72 (0.55 to 0.92); P=0.011). The effect was most pronounced among the predefined group that included 272 patients without previous insulin treatment and at a low cardiovascular risk (0.49 (0.30 to 0.80); P=0.004).

Conclusion: Insulin-glucose infusion followed by intensive subcutaneous insulin in diabetic patients with acute myocardial infarction improves long term survival, and the effect seen at one year continues for at least 3.5 years, with an absolute reduction in mortality of 11%. This means that one life was saved for nine treated patients. The effect was most apparent in patients who had not previously received insulin treatment and who were at a low cardiovascular risk.

Key messages

- Diabetes mellitus is common among patients with acute myocardial infarction
- Diabetic patients with myocardial infarction have a poor short and long term prognosis
- Poor metabolic control is common among diabetic patients with myocardial infarction
It is well established that patients with diabetes mellitus are more likely than patients without diabetes to die after an acute myocardial infarction. The increased mortality is seen both in the acute phase and during one year of follow up.1 2 3 Studies that followed up patients for more than one year all showed a continued increased mortality among patients with diabetes.4 5 6 7 8 9 The unfavourable prognosis of diabetic patients has mainly been attributed to more pronounced left ventricular dysfunction7 10 11 12 and a high likelihood of reinfarction, many of which are fatal.1 4 13 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 function, as well as purely metabolic factors causing more oxygen consuming use of free fatty acids during acute myocardial ischaemia.14

We previously showed that the one year mortality in diabetic patients with acute myocardial infarction can be reduced by 30% with acute administration of insulin and glucose followed by intensive treatment with multidose subcutaneous insulin.15 16 17 This report describes the long term effect on overall mortality of intensive insulin treatment in diabetic patients after an acute myocardial infarction.

Subjects and methods

Study design

A detailed description of the diabetes mellitus, insulin glucose infusion in acute myocardial infarction (DIGAMI) study, including design, definitions, and methods, has been given elsewhere.15 16 All patients admitted to the coronary care units of 19 Swedish hospitals were considered for inclusion if they had had an acute myocardial infarction within the preceding 24 hours combined with previously known diabetes mellitus and a blood glucose concentration >11 mmol/l or a similar blood glucose concentration without known diabetes mellitus. Patients who could not participate for reasons of health, refused to participate, lived outside the hospital catchment area, were enrolled in other studies, or had participated previously in DIGAMI were excluded. Remaining subjects were randomised blindly to one of two groups: insulin and glucose or control. The randomisation was performed as soon as possible after hospital admission (mean (SD) 13 (7) hours after onset of symptoms). Besides standard treatment in a coronary care unit, patients in the insulin-glucose group received an insulin-glucose infusion according to a predefined protocol for at least 24 hours. This was followed by subcutaneous insulin four times daily for at least three months. Control patients were treated according to standard practice. These patients did not receive any insulin unless clinically indicated.

Before randomisation the patients were classified as being at high risk if they fulfilled two or more of the following criteria: age >70 years; previous myocardial infarction; history of congestive heart failure; and current treatment with digitalis. Before randomisation the patients were stratified into one of four groups according to risk (high; low) and to previous antidiabetic treatment (insulin; no insulin). Predefined groups were: no insulin-low risk (n=272); no insulin-high risk (n=129); insulin-low risk (n=119); and insulin-high risk (n=100).

Concomitant drug treatment 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 and treatment with β blockers and aspirin were initiated as soon as possible.

The DIGAMI protocol was approved by the ethics committees at the Karolinska Institute and the Universities of Gothenburg, Linkoping, Lund, and Uppsala.
Details of patients
Altogether 1240 diabetic patients with suspected acute myocardial infarction were admitted during January 1990 to December 1993. Half of them were excluded because of the exclusion criteria, leaving 620 patients. A detailed report of exclusion criteria and characteristics of excluded patients has been given elsewhere. Of the 620 study patients, 314 were allocated to the control group and 306 to the infusion group. Table 1) gives details of the patients allocated to the two groups and shows that the groups were balanced.

| View this table: | Characteristics of patients before admission for myocardial infarction. Values are numbers of patients in each group unless stated otherwise |
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All patients were followed up prospectively for one year, with scheduled visits at three and 12 months after randomisation, when specific case record forms were completed. These included information on mortality and morbidity. After one year the patients were followed up by their physician by regular visits according to the patient's need. On 31 July 1995 the vital status of all patients was checked and verified by the physician responsible for the study in each participating centre. No patient was lost to follow up.

Statistics
Standard statistical methods were used. Values are presented as means (SD). The significance of the differences between the two groups was tested by Student's t test and Fisher's exact test. Differences within groups were tested by a paired test. For survival data the log rank test was used. The effect and its confidence interval was estimated by the relative hazards rate in a Cox analysis. Cumulative mortality curves were estimated by the Kaplan-Meier method. All these data were handled according to the intention to treat principle. The Cox model was used to adjust simultaneously for other factors. A two tailed P value less than 0.05 was considered significant.

Results
The mean (range) follow up time was 3.4 (1.6-5.6) years, and no patients were lost to follow up as regards mortality.

Treatment
During the period in hospital almost half of the patients were given thrombolysis. At the time of hospital discharge 496 (80%) patients were taking aspirin and 434 (70%) β blockers. Angiotensin converting enzyme inhibitors were given to 192 (31%) patients. Besides antidiabetic treatment, including insulin, there were no significant differences between the two groups in the treatment in hospital or during follow up. During the first year of follow up 13 patients in the infusion group and 16 in the control group had a percutaneous transluminal coronary angioplasty, and bypass surgery was performed in 33 patients in the infusion group compared with 35 in the control group. At discharge from hospital 266 (87%) patients in the infusion group were taking insulin treatment compared with 135 (43%) in the control group (P<0.0001). The corresponding numbers were 245 (80%) and 141 (45%) (P<0.0001) after three months and 220 (72%) and 141 (49%) after one year (P<0.0001).

Metabolic control
At randomisation the two groups did not differ in concentration of glycated haemoglobin (A1c, table 1). Haemoglobin A1c decreased significantly in both groups during follow up. The reduction was greater in the infusion group both at three (1.1 (SD 1.6%) v 0.4 (1.5%); P<0.0001) and 12 months (0.9 (1.9%) v 0.4 (1.8%); P<0.01). Fasting blood glucose one year after randomisation did not differ between the two groups.

In the low risk-no insulin group the corresponding haemoglobin A1c value at three months was (1.3 (1.8%) v 0.6 (1.5%); P<0.001) and at 12 months was (1.3 (1.9%) v 0.5 (1.5%); P<0.001).

Mortality
During the initial year of follow up, including deaths in hospital, 82 (26%) patients died in the control group compared with 58 (19%) in the insulin group. This corresponds to a relative reduction in mortality of 30% ($P=0.027$). Most of the reduction occurred after discharge from hospital. Only in patients without previous insulin treatment and at low cardiovascular risk (44% of all patients) was this reduction already significant during the hospital phase (from 12% in the control group to 5% in the infusion group; relative reduction 58%; $P<0.05$).

During the continued follow up there were 138 (44%) deaths in the control group compared with 102 (33%) in the infusion group. Figure 1) presents the mortality curves for all patients. After one year there was a separation between the curves, which tended to increase with time. The relative reduction in mortality at the end of follow up (mean (range) 3.4 (1.6-5.6) years) was 28% by the Cox model (95% confidence interval 8% to 45%; $P=0.011$).

Table 2) presents the long term mortality within the prestratified risk groups. The most apparent effect was achieved in the low risk group not taking insulin, with an absolute reduction in mortality of 15%, from 33% in the control group to 18% in the infusion group. This corresponds to a relative reduction of 51% (19% to 70%; $P=0.004$) by the Cox model. Figure 2) gives the mortality curves for this group.

**Table 2** Long term mortality according to insulin treatment and risk of death. Values are numbers (percentages) patients unless otherwise stated

![Fig 1](image1.png)

Actuarial mortality curves during long term follow up in patients receiving insulin-glucose infusion and in control group among total DIGAMI cohort. Absolute reduction in risk was 11%; relative risk 0.72 (0.55 to 0.92); $P=0.011$

![Fig 2](image2.png)

Actuarial mortality curves during long term follow up in patients receiving insulin-glucose infusion and among control group of patients at low risk who were not taking insulin before randomisation. Absolute reduction was 15%; relative risk 0.49 (0.30 to 0.81); $P=0.004$
Diabetes mellitus is an independent marker of morbidity and mortality after acute myocardial infarction.\textsuperscript{1, 8} The DIGAMI study has previously shown that the one year mortality in diabetic patients after an acute myocardial infarction could be reduced by 30\% with intensive insulin treatment and that this treatment tended to influence all cardiovascular causes of death favourably.\textsuperscript{16, 17} This report shows that this effect is sustained for more than three years and further supports the theory that metabolic control is of utmost importance in macrovascular death.

Study limitations
One limitation of this study is that exact information about insulin treatment during long term follow up is not available. However, 220 (72\%) in the infusion group and 154 (49\%) in the control group were taking insulin at one year. Our experience is that withdrawal of insulin treatment after more than one year is uncommon. There was a gradual increase in insulin treatment among control patients, presumably reflecting the natural course of non-insulin dependent diabetes.

Importance of metabolic control
As previously reported the reduction in mortality increased during the first year of follow up.\textsuperscript{16} After one year the curves were still separate, and this impression increased during late follow up. It was clearly evident in low risk patients without previous insulin treatment. This suggest that long term metabolic control by means of intensified insulin treatment contributed to the beneficial result in the infusion group. In the no insulin-low risk group, however, mortality was already significantly reduced by half during the time in hospital, indicating dual effects of the complete regimen. Several recent studies have reported that metabolic control measured as fasting blood glucose or haemoglobin A1c concentration is a major determinant of future development of coronary heart disease among patients with non-insulin dependent diabetes mellitus.\textsuperscript{19, 20, 21, 22} Cardiovascular events decreased by 40\% after intense treatment of patients with insulin dependent diabetes in the diabetes control and complications trial.\textsuperscript{23} In the current study 97\% of all deaths during the first year of follow up had cardiovascular causes, and there was a trend in reduction of all types of cardiovascular deaths including fatal reinfarctions in the intervention group.\textsuperscript{17} During the first year haemoglobin A1c concentration decreased in both groups but significantly more in the infusion group, suggesting that long term metabolic control is important in the prevention of macrovascular death in patients with diabetes mellitus.

Possible mechanisms
The varying effects in different risk groups are interesting. They show that patients who had not previously been treated with insulin and who had a comparatively low risk profile benefited the most. This is in agreement with Rogers \textit{et al}, who found the best treatment effect of glucose-insulin-potassium infusion in non-diabetic patients with a low Killip class and an overall low mortality.\textsuperscript{24} The effect in the no insulin-low risk group may be related to reduced ischaemic injury during the acute phase, protecting against subsequent development of myocardial dysfunction. This may be further enhanced by continued subcutaneous insulin treatment with subsequent improved metabolic control. Intense insulin treatment may restore impaired platelet function,\textsuperscript{26} correct the disturbed lipoprotein pattern,\textsuperscript{25} and decrease plasma activity of plasminogen activator inhibitor, which is high in diabetic patients.\textsuperscript{27} The extended insulin treatment, with its beneficial secondary metabolic effects, is one possible mechanism for the reduced long term mortality in the infusion group. Another possible explanation, in view of the open study design, is that the institution of insulin was paralleled by an improvement in general patient care. If this is the case, however, it should not be seen as a bias but rather as part of a comprehensive care programme for diabetic patients with myocardial infarction. The similarity in concomitant treatment (including revascularisation procedures) between the two groups makes this factor less likely as a major contributor. Future studies should be designed to elucidate whether an acute or a long term metabolic effect is responsible for the net result. They should also focus on specific pathophysiological mechanisms behind the beneficial effects we have seen.

In summary, insulin-glucose infusion followed by intensive subcutaneous insulin treatment in diabetic patients with acute myocardial infarction improves long term survival by nearly a third, and the effect seems to last for at least 3.5 years. Even more important the absolute reduction in mortality was 11\%, implying one saved life for nine patients treated according to the DIGAMI protocol. The reduction in mortality is most apparent in patients without previous insulin treatment and at a low cardiovascular risk.
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