

## ROLE OF INSULIN-GLUCOSE INFUSION IN OUTCOMES AFTER ACUTE MYOCARDIAL INFARCTION: THE DIABETES AND INSULIN-GLUCOSE INFUSION IN ACUTE MYOCARDIAL INFARCTION (DIGAMI) STUDY

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### ABSTRACT

**Objective:** To review the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study for findings regarding effects on morbidity and mortality.

**Results:** The DIGAMI trial was an intervention study that tested the hypothesis that initial intensive metabolic control by insulin-glucose infusion for at least 24 hours followed by long-term treatment with subcutaneously administered insulin improved the prognosis in patients with diabetes and acute myocardial infarction. Overall, the intensive approach reduced the long-term relative mortality (at 3.4 years of follow-up) by 25% in the insulin-treated group. Improved long-term survival was especially evident in the prestratified group of patients without prior insulin treatment, in whom the 3.4-year mortality reduction was 45%. Furthermore, a close correlation was noted between high blood glucose level at admission and mortality among the patients in the control group; this relationship was attenuated by intensive insulin treatment.

**Conclusion:** The DIGAMI study supports the theory that intensive metabolic care in patients with diabetes who have had an acute myocardial infarction improves the prognosis. The study, however, could not answer whether this result was due to the initial insulin-glucose infusion or to the long-term subcutaneous treatment with insulin. This question is currently being addressed in the DIGAMI-2 study. (*Endocr Pract.* 2004;10[Suppl 2]:13-16)

#### Abbreviations:

**ACE** = angiotensin-converting enzyme; **ATP** = adenosine triphosphate; **DIGAMI** = Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction; **FFA** = free fatty acids; **HbA1c** = hemoglobin A1c; **OASIS** = Organization to Assess Strategies for Ischemic Syndromes; **PAI-1** = plasminogen activator inhibitor-1

### BACKGROUND

#### Extent of the Problem

Until the past decade, the prevalence of diabetes mellitus was thought to be approximately 10% among patients who had had an acute myocardial infarction. Recent evidence suggests, however, that the prevalence is more likely approximately 20 to 25% (1,2); perhaps this projection is also an underestimation of the actual problem (see subsequent material). The prevalence of diabetes among patients with unstable angina and non-Q-wave myocardial infarction, the most frequent admission diagnosis in coronary care units, was 21% in the Organization to Assess Strategies for Ischemic Syndromes (OASIS) registry, but this figure varied widely among countries. For example, it exceeded 30% in the United States (3). Most reports used previously known and treated diabetes as the definition of the disease. This criterion may underestimate the actual influence of glucometabolic disturbances on the occurrence and outcome of acute coronary syndromes. A recent study, in which serial oral glucose tolerance testing was performed after acute myocardial infarction, reported that only a third of all patients had a normal glucose tolerance test result 3 months after the acute event (4). Accordingly, diabetes and insulin resistance are among the major risk factors for acute coronary syndromes.

#### Morbidity and Mortality

Early reports from unselected consecutive patient populations with acute myocardial infarction showed that patients with diabetes had a 1-year mortality of almost 50% (1). During the past decade, major achievements were made in acute coronary care; subgroup analyses from many studies have shown a substantial reduction in mortality among patients with and without diabetes. Nonetheless, a consistently excessive mortality prevails among patients with diabetes, with an adjusted relative risk increase of approximately 1.5 to 2.5. A recent cohort study consisting of more than 25,000 patients, with data collected during 1995 to 1998, found a 1-year mortality of approximately 30% among patients with diabetes who were older than 65 years. Mortality was lower in the younger age-groups, but the relative effect of diabetes on an unfavorable outcome was higher with decreased age.

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The odds ratio for 1-year mortality among patients with diabetes was 1.7 in the elderly group in comparison with almost 3.0 in those younger than 65 years (2). In addition, published evidence indicates that diabetes is a major independent risk factor for both short-term and long-term mortality among patients with unstable angina or non-Q-wave myocardial infarction. In the OASIS registry, diabetes was an independent predictor of mortality (relative risk, 1.6), as well as cardiovascular death, new myocardial infarction, stroke, and newly developed congestive heart failure. Interestingly, patients with diabetes without prior cardiovascular disease had the same event rates for any of these outcomes as did patients without diabetes who had previous cardiovascular disease (3). Furthermore, recent data from the second Fast Revascularization During Instability in Coronary Artery Disease (FRISC) trial also indicate that patients with diabetes still have a more than doubled event rate in comparison with patients without diabetes, despite implementation of modern revascularization strategies after an episode of unstable coronary artery disease (5).

#### **Possible Reasons for the Prognosis**

Review of the literature regarding the causes of death in patients with diabetes and acute myocardial infarction shows that the most common cause cited is failure of the myocardial pump (6,7). A potential mechanistic explanation for this failure is a more vulnerable noninfarct area, resulting in an impaired compensatory hemodynamic response to injury. This outcome may be due to metabolic perturbations associated with the diabetic state, or it may be related to an impaired vascular reserve. The second most cited cause of death is myocardial reinfarction, which could be attributable to more extensive coronary atherosclerosis or a tendency of patients with diabetes to be more susceptible to thrombus formation (or both) (1,6,8,9).

Insulin promotes glucose oxidation, which is known to be beneficial in the ischemic condition. An increase in the amount of available glycolytic substrate increases the anaerobic synthesis of adenosine triphosphate (ATP) and attenuates the ischemia-induced ATP decrease. Furthermore, investigators have suggested that agents supportive of glucose oxidation could reduce posts ischemic contractile dysfunction.

Increased levels of circulating free fatty acids (FFA) due to high sympathetic activity also characterize acute myocardial ischemia. Oxidation of FFA is potentially detrimental in the setting of myocardial ischemia because of an increased oxygen demand and a direct inhibition of glucose oxidation (which is favorable in the ischemic condition, as previously mentioned). Furthermore, increased utilization of FFA during ischemia also causes accumulation of toxic FFA metabolites, which may further induce membrane damage, provoke arrhythmias, and exacerbate mechanical dysfunction.

Patients with diabetes have impaired glucose oxidation and increased FFA utilization attributable to a relative or absolute insulin deficiency; hence, the aforementioned metabolic perturbations may be even more important in patients with diabetes than in other patients during an acute ischemic event. The posts ischemic myocardial contractile dysfunction and the increased frequency of overt heart failure reported in patients with diabetes may be a result of these metabolic derangements.

Some evidence also clearly indicates that insulin treatment in patients with diabetes could favorably affect the coagulation system. Diabetes is associated with enhanced platelet activation and aggregation, increased plasminogen activator inhibitor-1 (PAI-1) activity, and increased fibrinogen concentrations, among other aberrations of the coagulation system. Insulin therapy has been shown to reduce the increased production of thromboxane  $A_2$  and to decrease PAI-1 activity in patients with type 2 diabetes; therefore, it may positively influence the high reinfarction rate noted in this patient group (10,11). Data on clinical outcomes relative to these effects are not available.

#### **THE DIABETES AND INSULIN-GLUCOSE INFUSION IN ACUTE MYOCARDIAL INFARCTION STUDY**

##### **Study Design**

On the basis of the foregoing principles, it was postulated that administration of exogenous insulin during and after acute myocardial infarction in patients with diabetes would favorably influence the development of pump failure, the susceptibility to reinfarction, and therefore mortality. The Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study was designed to evaluate the effect of insulin therapy on survival in patients with diabetes who had had an acute myocardial infarction (12-15). Eligible patients were those with suspected acute myocardial infarction and an admission blood glucose level of more than 11 mmol/L (198 mg/dL), with or without known diabetes. Before randomization, all patients were stratified on the basis of cardiovascular risk and prior insulin treatment. Patients were randomized either to intravenous insulin-glucose infusion for at least 24 hours, followed by multidose subcutaneous insulin treatment for at least 3 months, or to a control group.

The protocol used "conventional treatment" for the control arm, which was left to the discretion of the treating physician; most patients in the control arm continued with their ongoing prerandomized treatment. The responsible study physician, however, could reinforce the antidiabetic treatment—that is, institute orally administered therapy or insulin treatment if clinically indicated. Prerandomized insulin treatment was never withdrawn in the control group. Standard therapy for acute myocardial infarction was applied to all subjects, and the protocol emphasized

the use of thrombolytic therapy when indicated (50% of enrolled patients), aspirin (80%), and  $\beta$ -adrenergic blocking agents (70%) as tolerated. The primary endpoint in the study was 3-month mortality, and the secondary endpoint was 1-year mortality.

### Characterization of Study Participants

During the enrollment period, 1,240 eligible patients were screened, half of whom were excluded on the basis of predefined exclusion criteria. The excluded patients, the preponderance of whom were female, were somewhat older than those who qualified for inclusion. These excluded patients were entered into a registry; their age-adjusted 1-year mortality was similar to that for the conventional therapy arm. The remaining 620 patients were randomized to the study. The groups were well balanced with regard to baseline characteristics. The mean age was 68 years, and approximately 60% were men. Notably, this was a rather ill population—40% had prior myocardial infarction, 50% had a history of angina, 50% had hypertension, 20% had previously diagnosed heart failure, and 23% were smokers. The mean duration of diabetes was 10 years, and the majority of patients had type 2 diabetes.

Approximately 45% of the patients were receiving oral antidiabetes therapy at enrollment, and about a third were receiving insulin. This stratification of diabetes treatment at study entry is representative of the current practice in Sweden. The mean admission hemoglobin A1c (HbA1c) was 8%, and the mean blood glucose value was 15.5 mmol/L (281 mg/dL); these findings were the same between treatment arms. No significant difference in serum potassium concentrations was noted between the study groups at presentation; however, there was a slight but expected decrease in the infusion group as a result of the effects of insulin on potassium flux.

### Results

The blood glucose curve in the group of patients who received infusion had a rather fast decline, with a mean blood glucose level of 7 mmol/L (126 mg/dL) by 6 hours. The curve then leveled off and eventually increased slightly. Fifteen percent of the infusion group (42 patients) had at least one episode of hypoglycemia, which was predefined as a blood glucose level of less than 3 mmol/L (54 mg/dL), with or without symptoms. Most patients did not report any symptoms during the hypoglycemia, and no direct harmful effects of hypoglycemia were noted immediately or during the 12 months of follow-up. The duration of stay in the hospital was almost 3 days longer for the infusion group than for the control group, presumably because of the need for injection training.

At the time of dismissal from the hospital, 80% of the study patients were receiving aspirin, and most of the remaining 20% were receiving warfarin. Treatment at dismissal included  $\beta$ -adrenergic blocking agents in 70% of all patients and angiotensin-converting enzyme (ACE) inhibitors in 30%. The beneficial effect of ACE inhibitors

became evident during the study; therefore, the patients receiving ACE inhibitors in the study represented a group with more severe congestive heart failure. No difference in these medications was evident between the study groups at hospital dismissal or during 12 months of follow-up.

The compliance with insulin treatment was good, and among all patients, almost 90% randomized to the infusion group were receiving insulin at hospital dismissal compared with 44% in the control group. At 1 year, more than 70% of the patients in the infusion group were still receiving insulin in comparison with about 50% of the control group. The increasing prevalence of use of insulin during the 12 months of follow-up in the control group presumably reflects the natural course of type 2 diabetes.

The difference regarding insulin treatment between the two study groups was even more pronounced among stratum 1 patients. In that predefined subgroup, which consisted of 272 patients without prior insulin treatment and at low cardiovascular risk, 81% randomized to the infusion group were receiving insulin at hospital dismissal compared with 15% in the control group. At 1 year, 66% of the infusion group were still receiving insulin compared with approximately 24% of the control group. This difference was also reflected by a significantly more pronounced absolute reduction in HbA1c after 1 year of  $-1.3\%$  compared with  $-0.5\%$  for the control group. Among all patients in the DIGAMI study, the reduction in HbA1c was  $-0.9\%$  in the infusion group compared with  $-0.4\%$  in the control group ( $P < 0.001$ ).

The mortality at 1 year was significantly reduced from 26% in the control group to 19% in the infusion group, with an early separation between the curves; this was a significant difference but with broad confidence intervals. The long-term data (3.4 years of follow-up) show a persistent relative mortality reduction of 25% ( $P = 0.011$ ) in the insulin-treated group. This corresponds to an absolute mortality reduction of 11%.

In reference to the predefined strata regarding cardiovascular risk and prior insulin use, the largest stratum included those patients without prior insulin treatment and at a low overall risk before randomization (stratum 1). These 272 patients were younger subjects who had been treated with orally administered antidiabetic agents (64%) or diet (15%) or who had newly diagnosed diabetes (21%), and they had approximately the same blood glucose control as patients in the other strata. As expected, the mortality was much lower in both groups within this stratum in comparison with that in the other strata. This group, however, demonstrated the largest effect from the insulin therapy. At hospital dismissal, patients in this stratum had a 58% reduction in mortality ( $P < 0.05$ ). This benefit was sustained throughout the follow-up, with a 50% reduction at 12 months. On assessment of long-term mortality, a further separation between the curves was observed within this stratum during the 3.4 years of follow-up, with a highly significant 45% reduction in mortality (33% versus 18%;  $P = 0.004$ ).

Multivariate analysis showed that age, previous heart failure, duration of diabetes, admission blood glucose, and admission HbA1c were independent predictors of mortality in the total DIGAMI cohort. Interestingly, the previously described close relationship between high admission blood glucose level and mortality was evident only among patients in the control group. This finding suggests that appropriate metabolic treatment during the peri-infarction period attenuated the harmful effect of a high blood glucose concentration on admission or perhaps a deranged metabolic state.

#### Immediate or Long-Term Effect?

The DIGAMI patients not only were subjected to an immediate metabolic intervention with infusion of insulin-glucose but also received multidose insulin treatment for long-term metabolic control. Thus, it is impossible to determine which part—immediate intervention or long-term meticulous metabolic control—contributed most to the favorable outcome or whether both elements of the treatment strategy were important (which may be hypothesized). This issue is currently being addressed in the ongoing DIGAMI-2 trial, which is expected to report findings this year (2004).

#### Study Limitations

The DIGAMI study does have limitations. The overall mortality was lower than was predicted in the power calculation during the design of the study; this result was probably due to the extensive use of concomitant evidence-based treatment within the study. This low mortality decreased the power of the study to detect a difference between the study groups at 3 months, which was the primary endpoint. Another limitation involves the issue of mechanism of benefit. Furthermore, the effect of the immediate therapy cannot be separated from that of the ongoing therapy throughout the course of the study. In addition, it is possible that orally administered agents are detrimental, and a potential interpretation could be that oral hypoglycemic therapy was actually causing harm rather than insulin causing benefit. Some of these limitations are addressed in the DIGAMI-2 trial.

#### CONCLUSION

Several recent epidemiologic reports suggest that hyperglycemia per se is a determinant for the development of cardiovascular disease in patients with diabetes. Biochemical perturbations related to diabetes, insulin resistance, and hyperglycemia may also be of major importance during the acute infarction period in conjunction with subsequent impaired myocardial hemodynamic response to the injury. Furthermore, they may increase the risk for early reocclusion. Theoretically, strict metabolic control by means of insulin treatment could improve these metabolic alterations; data from the DIGAMI study support this theory.

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