European Heart Journal (1996) **17**, 1337–1344

Effects of insulin treatment on cause-specific one-year mortality and morbidity in diabetic patients with acute myocardial infarction

K. Malmberg*, L. Rydén*, A. Hamsten†, J. Herlitz‡, A. Waldenström§ and H. Wedel¶ on behalf of the DIGAMI study group

*Departments of *Cardiology and †Medicine, Karolinska Sjukhuset, Stockholm, ‡Department of Medicine, Sahlgrenska Sjukhuset, Göteborg, §Department of Medicine, Norrlands Universitetssjukhus, Umeå and ¶Nordiska Hälsovårdshögskolan Göteborg, Sweden*

Diabetic patients with acute myocardial infarction have a poor prognosis, which has been attributed to a higher incidence of congestive heart failure and fatal reinfarction. This study reports on the one-year morbidity and mortality in a randomized study with the aim of testing whether insulin–glucose infusion initiated as soon as possible after onset of myocardial infarction and followed by long-term subcutaneous insulin treatment may have a beneficial effect on outcome in diabetic patients. In all, 306 patients were recruited to the insulin-treated group, while 314 patients served as controls.

The overall mortality after one year was 19% in the insulin group compared to 26% among controls ($P<0.05$). The treatment effect was most pronounced in patients without prior insulin medication and at low cardiovascular risk. In this stratum the in-hospital mortality was reduced by 58% ($P<0.05$) and the one-year mortality by 52% ($P<0.02$).

The most frequent cause of death in all patients was congestive heart failure (66%), but cardiovascular mortality (congestive heart failure, fatal reinfarction, sudden death and stroke) tended to be decreased in insulin-treated patients. However, this difference did not reach the level of statistical significance. The number of reinfarctions was 53 (28% fatal) in the insulin group compared to 55 (45% fatal) in the control group. The two groups did not differ as regards need for hospital care or coronary revascularization during the year of follow-up.

In summary, left ventricular failure and fatal reinfarctions contribute to increased mortality in diabetic patients following acute myocardial infarction. Intensive insulin treatment lowered this mortality during one year of follow-up. **(Eur Heart J 1996; 17: 1337–1344)**

Key Words: Diabetes mellitus, acute myocardial infarction, insulin treatment, morbidity, mortality, prognosis.

Introduction

Patients with diabetes mellitus have increased short- and long-term mortality after myocardial infarction compared to non-diabetics[1–4]. The unfavourable prognosis of diabetic patients has mainly been attributed to a more pronounced left ventricular dysfunction, with a high occurrence of cardiogenic shock and congestive heart failure[3,5–7]. This may relate to an increased fatty acid metabolism compromising myocardial glucose oxidation both in ischaemic and in non-ischaemic areas. Insulin suppresses fatty acid mobilization and beta-oxidation, thereby enhancing the more energy saving glucose utilization[8]. Following hospital discharge the difference in morbidity and mortality between diabetics and non-diabetics becomes even more apparent. This seems in particular to relate to a high incidence of fatal reinfarctions[1,4,7,9,10].

Patients with diabetes mellitus are characterized by impaired platelet and fibrinolytic functions[11,12]. Insulin reduces the production of thromboxane-A and decreases plasma plasminogen activator inhibitor-1 activity (PAI-1; 11,13), known risk markers for recurrent infarction in patients with non-insulin dependent diabetes. Thus insulin treatment may improve prognosis after myocardial infarction in the diabetic patient.

The Diabetes Insulin-Glucose in Acute Myocardial Infarction (DIGAMI) study recently demonstrated that insulin–glucose infusion followed by multidose insulin treatment reduces one-year mortality in diabetic patients with acute myocardial infarction, in particular

Revision submitted 13 January 1996, and accepted 15 February 1996.

Correspondence: Klas Malmberg, MD, Department of Cardiology, Karolinska Hospital, Box 110, S-171 76 Stockholm, Sweden.

0195-668X/96/091337+08 $18.00/0

among non-insulin dependent diabetes patients without previous insulin treatment[14].

This paper reports on the influence of insulin therapy on early and long-term cause-specific mortality and morbidity, with special reference to fatal and non-fatal reinfarctions.

Material and methods

A detailed description of DIGAMI including study design, definitions and methods has been published elsewhere[14,15]. Briefly, this is a multicentre randomized study on the effect on mortality and morbidity of an intravenous infusion of insulin–glucose to patients with suspected acute myocardial infarction and diabetes mellitus. The infusion was initiated as soon as possible and continued until stable normoglycaemia was attained and at least for 24 h. It was followed by a 3 months minimum of four-dose subcutaneous insulin therapy.

All patients were followed prospectively with scheduled visits at the out-patient clinic 3 and 12 months after randomization.

Definitions

Diabetes mellitus

Diabetes mellitus was considered present if a patient had been informed of this diagnosis and was on treatment (diet, tablets or insulin). Patients with no previous diagnosis of diabetes mellitus but with a blood glucose ≥ 11 mmol . l^{-1} on admission were classified as having newly detected diabetes mellitus. These patients were also included. Patients were classified as non-insulin-dependent or insulin-dependent by clinical history according to the definitions of the National Diabetes Data Group[16]. Thus non-insulin dependent diabetes patients were usually older than 40 years at diagnosis, had not required insulin for 2 years after the diagnosis and were not prone to ketosis.

Myocardial infarction

The diagnosis 'definite myocardial infarction' required that at least two of the following criteria were fulfilled: (1) Chest pain of at least 15 min duration; (2) At least two values of serum creatine kinase and serum creatine kinase B above the normal range (normal value +2 SD) 10–16 h after onset of symptoms or at least two serum Lactic dehydrogenase values +2 SD above the normal range 48–72 h after onset of symptoms, including an iso-enzyme pattern typical of myocardial infarction; (3) Development of new Q waves in at least two of the 12 standard ECG leads.

A reinfarction was defined as an event fulfilling the criteria given for a myocardial infarction but appearing later than 72 h after the index infarct. The hospital files for all patients with a suspected reinfarction were checked and the diagnosis approved by two independent cardiologists who were not in any other way related to the study. The final analysis comprised the first reinfarction only.

Sudden death was unwitnessed death or death within 24 h of symptoms.

Ventricular tachyarrhythmias

The presence of either ventricular premature beats or ventricular tachycardia requiring antiarrhythmic treatment, or documented ventricular fibrillation were included. Ventricular fibrillation was defined as early if it occurred within 48 h of the onset of symptoms and late if it occurred thereafter.

Atrioventricular block

Only high-grade AV-blocks (II–III) were considered. Standard ECG criteria were applied. The conduction defect had to be treated in some way to be noted in the case record form.

Congestive heart failure

Clinical and/or radiological signs of pulmonary congestion resulting in the institution of treatment.

Study design

All patients admitted to the coronary care units of 19 Swedish hospitals[14] with suspected acute myocardial infarction within the preceding 24 h and with diabetes mellitus according to given definitions were considered for inclusion.

Prior to randomization, the patients were stratified into one of four groups according to a risk classification based on a history of previous infarction, presence of congestive heart failure, age (old; young) and previous antidiabetic treatment (insulin; no insulin). Predefined strata were: (1) No insulin, low risk; (2) No insulin, high risk; (3) Insulin, low risk; (4) Insulin, high risk.

Patients randomized to insulin treatment (infusion group) received an insulin–glucose infusion followed by multidose 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. Besides the administration of insulin all patients were managed according to predefined guidelines. If there were no contraindications thrombolysis, beta-blockade and aspirin were given as early as possible. Particular measures were taken to achieve as uniform treatment as possible within the two groups, except for the use of insulin, utilizing written treatment guidelines and repeated education sessions. A flow-chart of the study design is given in Fig. 1, and the insulin–glucose infusion protocol is provided in Table 1.

All patients were followed for one year. Specific case record forms were completed 3 and 12 months after

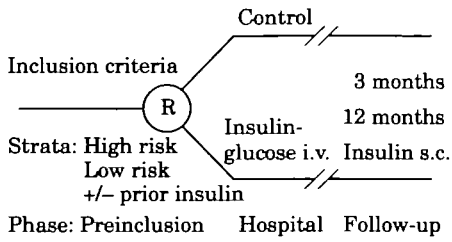

Figure 1 **Schematic presentation of the DIGAMI study protocol.**

randomization. These included information on mortality and morbidity. No patient was lost to follow-up.

Patient material

Altogether 1240 diabetic patients with suspected acute myocardial infarction were admitted to the coronary care unit(s) during the recruitment period between January 1990 and December 1993. Half of them were excluded due to predefined exclusion criteria, leaving 620 patients who comprise the present material. A detailed report of exclusion criteria and characteristics of excluded patients has been given elsewhere[14]. Of the 620 study patients, 314 were allocated to the control group and 306 to the infusion group, respectively. Pertinent patient characteristics, as presented in Table 2, demonstrate that the groups were well balanced.

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. Differences within groups were tested by a paired test. For survival data the log-rank test was used. Cumulative mortality curves are estimated by the Kaplan–Meier method. To adjust for confounding factors the Cox model was used. A two-tailed P-value less than 0·05 was considered statistically significant.

Results

Treatment

The initial hospital phase was 11·3 ± 13·3 (mean ± SD) days for patients in the infusion group and 9·5 ± 9·4 days for those in the control group (P=0·043). This difference related to time for insulin injection training. 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 one year (P<0·0001), respectively. Other than the administration of insulin, the two groups did not differ as regards pharmacological therapy. Both groups were treated intensively both during the hospital phase and the subsequent period of follow-up. Fifty percent of the patients were thrombolysed, a similar proportion received intravenous nitroglycerin (54%) and 17% were fully heparinized during the acute period in hospital. At the time of hospital discharge, 80% of the patients were on aspirin and 68% on beta-blockade (metoprolol). ACE inhibitors were given to 31% of the patients.

Mortality

Mortality figures are given in Table 3. After one year the total mortality had decreased by 30% in the infusion group (P=0·027). Most of the reduction occurred after discharge from hospital. Among patients without prior insulin treatment and at low cardiovascular risk (Stratum 1) mortality had significantly reduced during the hospital phase and this was maintained throughout the period of follow-up (Fig. 2).

Table 1 Protocol used by the CCU nurses for the insulin–glucose infusions

Infusion: 500 ml 5% glucose with 80 IU of soluble insulin (approximately 1 IU . 6 ml^{-1}).

Start with 30 ml . h^{-1}. Check blood glucose after 1 h. Adjust infusion rate according to the protocol and aim for a blood glucose level of 7–10 mmol . l^{-1}. Blood glucose should be checked after 1 h if the infusion rate has been changed, otherwise every 2 h. If the initial fall in blood glucose exceeds 30%, the infusion rate should be left unchanged if blood glucose is higher than 11 mmol . l^{-1} and reduced by 6 ml . h^{-1} if blood glucose is within the targeted range of 7–10·9 mmol . l^{-1}.

If blood glucose is stable ≤10·9 mmol . l^{-1} after 2200 h, reduce infusion rate by 50% during the night.

B-glucose >15 mmol . l^{-1}:	Give 8 IU of insulin as an i.v. bolus injection and increase infusion rate by 6 ml . h^{-1}.
11–14·9 mmol . l^{-1}:	Increase infusion rate by 3 ml . h^{-1}.
7–10·9 mmol . l^{-1}:	Leave infusion rate unchanged.
4–6·9 mmol . l^{-1}:	Decrease infusion rate by 6 ml . h^{-1}.
<4 mmol . l^{-1}:	Stop infusion for 15 min. Then test B-glucose and continue testing every 15 min until B-glucose ≥7 mmol . l^{-1}. In the presence of symptoms of hypoglycaemia, administer 20 ml 30% glucose i.v. The infusion is resumed with an infusion rate decreased by 6 ml . h^{-1} when B-glucose ≥7 mmol . l^{-1}.

Table 2 Pre-hospital characteristics. Numbers and percentages of patients in each group if not otherwise stated

Parameter	Control group (n=314)		Infusion group (n=306)		P
	no	%	no	%	
Age (years, mean ± SD)	68 ± 9		67 ± 9		ns
Sex					
Male	197	63	191	62	ns
Female	117	37	115	38	ns
BMI (kg . m^{-2}; mean ± SD)	27 ± 4		27 ± 4		ns
Previous diseases					
Myocardial infarction	117	37	121	40	ns
Angina pectoris	164	52	176	58	ns
Hypertension	154	49	143	47	ns
Congestive heart failure	70	22	69	23	ns
Type of diabetes mellitus					
Non-insulin-dependent	265	84	251	82	ns
Insulin-dependent	49	16	55	18	ns
Previously unknown	47	15	31	10	ns
Duration (years; mean ± SD)	10 ± 10		10 ± 10		ns
Anti-diabetic treatment					
None	47	15	31	10	ns
Diet	39	12	33	11	ns
Tablets	115	37	140	46	ns
Insulin	113	36	102	33	ns
Blood glucose at randomization (mmol . l^{-1})	15·7 ± 4·2		15·4 ± 4·1		ns
$HbA1_c$ at randomization (%)	8·0 ± 2·0		8·2 ± 1·9		ns
Blood glucose 24 h after randomization (mmol . l^{-1})	11·7 ± 4·1		9·6 ± 3·3		<0·0001
Blood glucose at hospital discharge (mmol . l^{-1})	9·0 ± 3·0		8·2 ± 3·1		<0·01
Serum potassium at randomization (mmol . l^{-1})	4·3 ± 0·5		4·3 ± 0·5		ns
Serum potassium after 24 h (mmol . l^{-1})	4·2 ± 0 5		4·0 ± 0·4		<0·001

Table 3 Mortality and specific cause of death during one year of follow-up. Percentages within parentheses

	Total n=620	Control n=314	Infusion n=306	P
Mortality				
Hospital	63 (10)	35 (11)	28 (9)	ns
Discharge—12 months	77 (13)	47 (15)	30 (10)	<0·05
Total	140 (23)	82 (26)	58 (19)	<0·05
Causes of death				
Heart failure	93	51	42	ns
Sudden death	22	16	6	ns
Myocardial rupture	6	3	3	ns
Stroke	10	7	3	ns
Non classified	4	2	2	ns
Non cardiovascular	5	3	2	ns

The specific causes of death are outlined in Table 3. Most patients died of congestive heart failure (66%). There was a trend towards less cardiovascular deaths of all kinds, and specifically for sudden death, in the insulin group compared to the control group. However, this trend did not reach the level of statistical significance.

Morbidity

During hospitalization the control group did not differ from the infusion group regarding the incidence of reinfarctions (4% vs 5%), ventricular fibrillations (5% vs 3%), high degree atrioventricular conduction disturbances (3% vs 7%) or congestive heart failure (48% vs 50%).

The occurrence of reinfarction is given in Fig. 3. During the year of follow-up, 108 patients (18%) suffered a reinfarction (55 controls and 53 in the insulin group; ns). The cumulative rate of fatal reinfarctions is given in the lower part of Fig. 3. After one year the curves separate with 25 fatal reinfarctions among the control patients compared to 15 in the insulin group. This corresponds to a reduction of 40% (95% confidence interval − 15% to 68%; P=0·12). In all, 45% of the reinfarctions were fatal in the control group compared to 28% in the insulin group (ns).

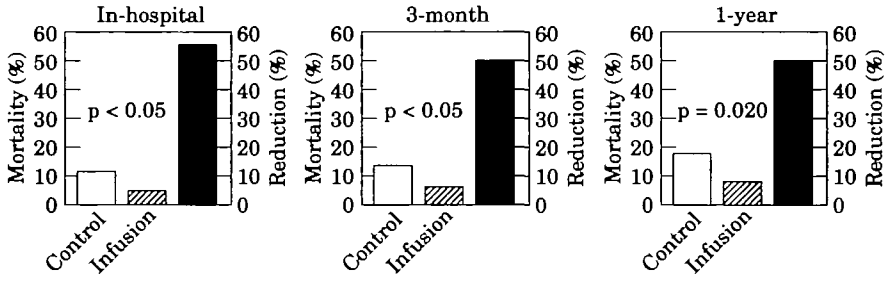

Figure 2 **In-hospital, 3-month and one-year mortality in patients belonging to stratum 1 (n=272).**

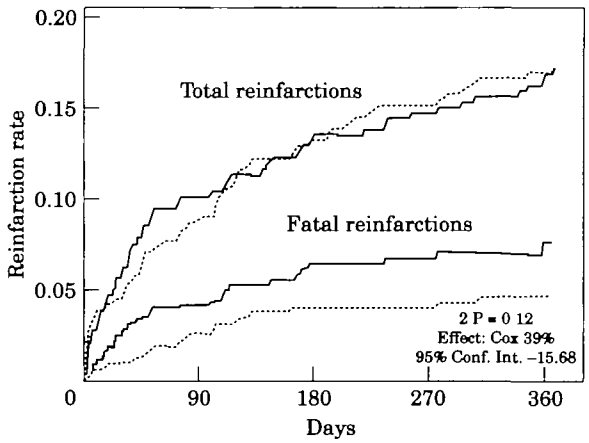

Figure 3 **Cumulative reinfarction rate during the year of follow-up. ——=control; – – –=infusion.**

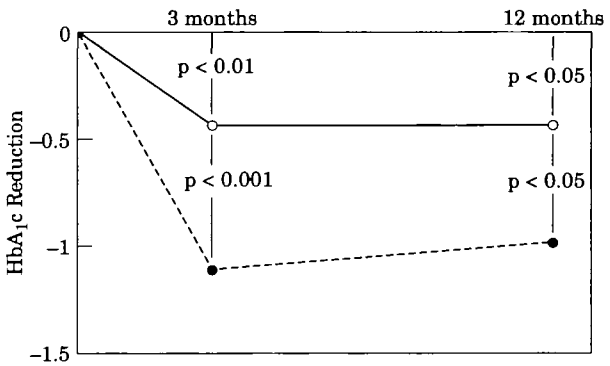

Figure 4 **Reduction in glycated haemoglobin ($HbA1_c$) during the year of follow-up. ●=patient group; ○=control group.**

Table 4 Need for hospitalization and revascularization during one year of follow-up

Parameter	Control n=314	Infusion n=306	*P*
Total hospital days (range)	3214 (0–270)	3129 (0–275)	ns
Hypoglycaemia (patients)	3	8	ns
Hospitalization due to hypoclycaemia (days)	30	34	ns
Hospitalization due to heart failure (patients)	69	57	ns
Revascularization (patients)			
Coronary angioplasty	16	13	ns
By-pass surgery	35	33	ns

The two groups did not differ as regards need for rehospitalization (Table 4). In particular in the infusion group, there was no increase due to hypoglycaemia and there was a tendency to fewer hospitalizations as a result of congestive heart failure. In contrast, 16% of all patients were referred to coronary revascularization with no difference between the two groups (Table 1).

Metabolic control

At randomization, glycated haemoglobin ($HbA1_c$; Table 2) did not differ between the two groups, but it decreased significantly in both groups during follow-up. The reduction was greater in the infusion group both at 3 (1·1 ± 1·6%, vs 0·4 ± 1·5%; $P<0·0001$) and 12 months (0·91 ± 1·9% vs 0·4 ± 1·8%; $P<0·01$; Fig. 4). Fasting blood glucose one year after randomization did not differ between the two groups.

Discussion

The DIGAMI study demonstrates that long-term mortality in diabetic patients with acute myocardial infarction may be reduced by insulin treatment and that this therapeutic regimen seems to beneficially influence all cardiovascular causes of death. The morality rate in the control group was well below that reported in previous studies[1,17]. This result was obtained despite the fact that pre-hospital characteristics clearly demonstrated that many DIGAMI patients were at high risk. The favourable result in controls as well may relate to intensive overall peri- and post infarction treatment, in particular a liberal use of thrombolysis and beta-blockade. Indeed, previous reports indicate that such therapy may be of a particular value for diabetic

patients[18–20]. However, there are reasons to believe that, due to a fear of complications and side-effects, beta-blockers and thrombolysis may have been instituted less frequently among diabetic patients[21–25,39]. The present protocol, emphasizing the importance of the proper use of these drugs, may explain this part of the results.

Study limitations

The unexpectedly low overall mortality made the study statistically less powerful than originally intended. Due to a type II error this limitation obviously blunted the possibilities of discovering differences between the two study groups with respect to causes of death and fatal reinfarctions. However, trends are consistent and logical in the light of the overall significant effect of insulin treatment on mortality. Thus, the data should permit a discussion of possible mechanisms and factors of potential significance for exploration in future studies.

By necessity DIGAMI was planned as an open study. It was felt unjustifiable to initiate blinded insulin–glucose infusions, and the first blood glucose recording anyhow would have disclosed the treatment allocation of most patients. It was not considered possible to conduct the study without regulating the infusion rate in relation to achieved blood glucose levels. Furthermore, some patients in the control group, for obvious reasons, received insulin treatment as well. The use of insulin in the infusion group, on the other hand, was very consistent during the year of follow-up, and the metabolic control within this group was significantly better than that among control patients. The somewhat improved metabolic control within the latter group, at least partly depending on insulin treatment, would, if anything, make it more difficult to demonstrate the benefits of insulin–glucose infusion followed by multidose subcutaneous insulin. Thus, it may be assumed that the observed differences in a such direction may, if anything, have been underestimated.

Concomitant therapy

Besides the administration of insulin the two groups were very similar as regards concomitant therapy. Thus, it is not possible to explain the difference in outcome between the infusion and the control groups by a variable use of drugs. Furthermore, almost the same number of patients in each group were referred for coronary revascularization. Contrary to what may have been expected, there were also no differences in hospitalization time during follow-up between the groups in spite of the institution of insulin treatment in a relatively old diabetic population.

Mortality

The overall mortality reduction increased gradually, as previously reported, during the year of follow-up[14]. This suggests that long-term metabolic control by means of intensified subcutaneous insulin treatment contributed to the beneficial results within the infusion group. This assumption is, however, to some extent contradicted by the results among the low-risk patients without prior insulin treatment. In this stratum mortality had already been reduced by more than 50% during the hospital phase and this effect was maintained throughout the entire follow-up period. Kuusisto and co-workers[26] recently reported that metabolic control measured as glycated haemoglobin ($HbA1_c$) is a major determinant of future coronary heart disease among patients with non-insulin dependent diabetes. Likewise, cardiovascular events were reduced 40% by intensive treatment of insulin-dependent diabetics in the Diabetes Control and Complications Trial[27]. These studies support the notion that long-term metabolic control is important in preventing macrovascular complications. The observed trend towards less mortality as a result of congestive heart failure, fewer sudden deaths and fewer strokes among the insulin-treated patients in the DIGAMI study further supports this evidence. In the present study, $HbA1_c$ decreased in both groups, but significantly more in the insulin-treated group.

Congestive heart failure accounted for 66% of all deaths. Several previous studies have shown an increased frequency of left ventricular failure among diabetic patients during and after acute myocardial infarction[5–7]. There are also reports showing decreased function in the non-infarcted area among diabetics with myocardial infarction[3,28]. Although not statistically significant, the DIGAMI study demonstrated a trend towards fewer deaths from heart failure and fewer patients hospitalized due to heart failure within the insulin-treated group. This indicates that intense and prolonged insulin treatment may improve metabolism in non-infarcted areas of the myocardium, thereby possibly reducing the remodelling process, as have also been assumed by other authors[8,29].

Fewer patients died suddenly in the insulin group compared to the control group. Sudden cardiac death is common among diabetic patients and may account for 33% of the deaths of those with signs of autonomic dysfunction[30]. Although some of these sudden deaths may be due to arrhythmia secondary to silent myocardial ischaemia, there is evidence that some diabetics died suddenly in the absence of significant coronary artery disease[30]. Diabetic patients have a relative decrease in vagal tone during the period of the day when the incidence of sudden death is particularly high[31]. Poorly controlled diabetics are characterized by increased levels of catecholamines and serum free fatty acids[32]. Both these factors are related to death and arrhythmia following acute myocardial infarction[33–35]. Thus, improved metabolic control secondary to insulin therapy may exert beneficial effects by reducing serum free fatty acids and catecholamines.

Morbidity

Recurrent myocardial infarction is a major cause of hospitalization and late mortality following myocardial infarction. Almost all studies evaluating the incidence of reinfarction have revealed an increased rate of such events among diabetics compared with non-diabetics[4,7,10,36]. This may relate to increased platelet reactivity and decreased fibrinolytic function, the latter mainly due to increased plasma levels of PAI-1[11,37,38]. In the present study, the infusion group was treated with multidose subcutaneous insulin for at least 3 months. Part of the rationale for this treatment was the finding that insulin reduces platelet-derived tromboxane A_2 production and PAI-1 activity in patients with non-insulin dependent diabetes[11,13]. Accordingly it was hypothesized that such a regimen may reduce the risk of recurrent infarctions. However, there was no difference in the rate of reinfarctions between the two groups during the year of follow-up. Interestingly, fatal reinfarctions seemed to be reduced. Lack of statistical power may explain why this 40% reduction did not make a statistically significant difference. However, in the light of previous studies that documented an increased occurrence of lethal reinfarctions among diabetics[1,9], this is an interesting finding. Most patients with fatal reinfarctions died from congestive heart failure. A possible mechanism may be that insulin therapy increased glucose metabolism, thereby making that myocardium more refractory to recurrent ischaemia. Another explanation could be increased glucose oxidation providing metabolic support to the non-ischaemic areas during and after recurrent ischaemia, as already discussed. It may also be speculated that insulin positively influenced the proneness to thrombus formation by reducing platelet and antifibrinolytic activity. This may decrease the tendency to develop total coronary occlusions. The latter mechanisms may also explain the tendency towards protection against fatal strokes among insulin-treated patients. Indeed, it has been claimed that stroke after myocardial infarction is more common in diabetic patients than in non-diabetics[40].

Conclusions

Insulin–glucose infusion followed by subcutaneous insulin treatment in patients with diabetes mellitus and acute myocardial infarction favourably influences one-year mortality by reducing all cardiovascular causes of death. This therapeutic regimen seems to have a particular impact on fatal reinfarctions. Data from the DIGAMI study suggest that the overall metabolic state, with its ultimate effects on the vessel walls and the myocardium, determines the prognosis of the diabetic patient with myocardial infarction and should accordingly be appropriately handled.

The authors express their gratitude to Rolf Nordlander, MD, and Göran Sundlöf, MD, for the independent evaluation and classification of the reinfarctions. We are also grateful to Anneli Iwarsson, RN, who skilfully monitored the study. The DIGAMI study was supported by the Swedish Heart-Lung Foundation, Hoechst AG and Karolinska Institutet.

References

[1] Malmberg K, Rydén L. Myocardial infarction in patients with diabetes mellitus. Eur Heart J 1988; 9: 256–64.
[2] Herlitz J, Malmberg K, Karlsson B, Rydén L, Hjalmarsson Å. Mortality and morbidity during a five year follow-up of diabetics with myocardial infarction. Acta Med Scand 1988; 24: 31–8.
[3] Granger C, Califf R, Young S *et al.* Outcome of patients with diabetes mellitus and acute myocardial infarction treated with thrombolytic agents. J Am Coll Card 1993; 21: 920–5.
[4] Karlson BW, Herlitz J, Hjalmarson A. Prognosis of acute myocardial infarction in diabetic and non-diabetic patients. Diabet Med 1993; 10: 449–54.
[5] Singer D, Moulton A, Nathan D. Diabetic myocardial infarction. Interaction of diabetes with other preinfarction risk factors. Diabetes 1989; 38: 350–7.
[6] Jaffe A, Spadaro J, Schechtman K, Roberts R, Geltman E, Sobel B. Increased congestive heart failure after myocardial infarction of modest extent in patients with diabetes mellitus Am Heart J 1984; 108: 31–7.
[7] Stone P, Muller J, Hartwell T *et al.* The effect of diabetes mellitus on prognosis and serial left ventricular function after acute myocardial infarction: contribution of both coronary disease and diastolic left ventricular dysfunction to the adverse prognosis. J Am Coll Card 1989; 14: 49–57.
[8] Rodrigues B, McNeill JH. The diabetic heart: metabolic causes for the development of a cardiomyopathy. Cardiovasc Res 1992; 26: 913–22.
[9] Savage M, Krolewski A, Kemien G, Lebeis M, Christlieb R, Lewis S. Acute myocardial infarction in diabetes mellitus and significance of congestive heart failure as a prognostic factor. Am J Cardiol 1988; 62: 665–9.
[10] Barbash GI, White HD, Modan M, van de Werf F. Significance of diabetes mellitus in patients with acute myocardial infarction receiving thrombolytic therapy. J Am Coll Card 1993; 22: 707–13.
[11] David G, Catalan I, Averna M *et al.* Tromboxane biosynthesis and platelet function in Type II diabetes mellitus. N Engl Med 1990; 322: 1769–74.
[12] Vague D, Raccah D, Juhan-Vague I. Hemobiology, vascular disease and diabetes with special reference to impaired fibrinolysis. Metabolism 1992; 41 (Suppl): 2–6.
[13] Jain SK, Nagi DK, Slavin BM, Lumb PJ, Yudkin JS. Insulin therapy in type 2 diabetic subjects suppresses plasminogen activator inhibitor (PAI-1) activity and proinsulin-like molecules independently of glycaemic control. Diabet Med 1993; 10: 27–32.
[14] Malmberg K, Rydén L, Efendic S *et al.* A randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction: Effects on one year mortality. J Am Coll Cardiol 1995; 26: 57–65.
[15] Malmberg K, Efendic S, Rydén L. Feasibility of insulin-glucose infusion in diabetic patients with acute myocardial infarction. Diabetes Care 1994; 17: 1007–14.
[16] National Diabetes Data Group. Classifications and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 1979; 28: 1039–57.
[17] Yudkin J, Oswald G. Determinants of hospital admissions and case fatality in diabetic patients with myocardial infarction. Diabetes Care 1988; 11: 351–8.
[18] Fibrinolytic Therapy Trialists (FFT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Lancet 1994; 343: 311–22.

[19] Malmberg K, Herlitz J, Hjalmarsson Å, Rydén L. Effects of metoprolol on mortality and late infarction in diabetics with suspected acute myocardial infarction. Retrospective data from two large scale studies. Eur Heart J 1989; 10: 423–8.
[20] Gundersen T, Kjekshus J. Timolol treatment after myocardial infarction in diabetic patients. diabetes Care 1983; 6 285–90.
[21] Umachandran V, Ranjadayalan K, Kobelman P, Timmis A. Thrombolytic therapy in high risk subgroups: morbidity and mortality benefits in diabetics and the elderly. Eur Heart J 1991; 12 (Suppl): 321.
[22] APBI, Data Sheet Compendium. Data sheet Streptase. Datapharm publications 1991–1992; 584–586.
[23] Helgeland A, Leren P, Foss O, Hjerman I, Holme I, Lund-Larsen I. Serum glucose levels during long-term observation of treated and untreated men with mild hypertension. Am J Med 1984; 76: 802–5.
[24] William-Olson T, Fellenius E, Björntorp P, Smith U. Differences in metabolic responses to beta-adrenergic stimulation after propranolol and metroprolol administration. Acta Med Scand 1979; 205: 201–9
[25] Deacon S, Karunanayake A, Barnett D. Acebutolol, atenolol and propranolol and metabolic responses to acute hypoglycaemia in diabetes. Br Med J 1977; 2: 1255–7.
[26] Kuusisto J, Mykkänen L, Pyörälä K, Laakso M. NIDDM and its metabolic control predict coronary heart disease in elderly subjects. Diabetes 1994; 43: 960–7.
[27] The Diabetes Control and Complication Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus N Engl J Med 1993; 329: 977–86.
[28] Iwasaka T, Takahashi N, Nakamura S *et al.* Residual left ventricular pump function after acute myocardial infarction in NIDDM patients. Diabetes Care 1992; 14: 1522–6.
[29] Katz A. Cardiomyopathy of overload. N Engl J Med 1990; 322: 100–10.
[30] Ewing D. Cardiac autonomic neuropathy. In: Jarret R, ed. Diabetes and heart disease. Amsterdam: Elsevier, 1984: 99–132.
[31] Bernardi L, Ricordi L, Rossi M *et al.* Impairment of modulation of symphatovagal reflexes in diabetes: an explanation for sudden death? Circulation 1989; 80 (Suppl): II–1564.
[32] Christensen N. Plasma norepinephrine and epinephrine in untreated diabetics, during fasting and after insulin administration. Diabetes 1974; 23: 1–8.
[33] Oliver M, Kurien V, Greenwood T. Relation between serum free fatty acids and arrhythmias and death after acute myocardial infarction. Lancet 1968; 1: 710–15.
[34] Gupta D, Young R, Jewitt D, Harlog M, Opie L. Increased plasma free fatty acids concentrations and their significance in patients with acute myocardial infarction. Lancet 1969; 2: 1209–13.
[35] Tansey M, Opie L. Relations between plasma free fatty acids and arrhythmias within the first twelve hours of acute myocardial infarction. Lancet 1983; 1: 419–22.
[36] Ulvenstam G, Åberg A, Bergstrand R *et al* Long-term prognosis after myocardial infarction in men with diabetes mellitus. Diabetes 1985; 34. 787–92.
[37] Walmsley D, Hampton K, Grant P. Contrasting fibrinolytic response in type 1 (insulin-dependent) and type 2 (non-insulin-dependent) diabetes. Diabetic Med 1991; 8: 954–9.
[38] Hamsten A, Walldius G, Szamosi A *et al.* Plasminogen activator in plasma: risk factor for recurrent myocardial infarction. Lancet 1987; 2· 3–9
[39] Pfeffer M, Moye L, Braunwald E. Selection bias in the use of thrombolytic therapy in acute myocardial infarction. JAMA 1991; 266· 528–32.
[40] Pullicino P, Xuereb M, Aquilina J, Piedmonte M. Stroke following acute myocardial infarction in diabetics. J Int Med 1992; 231: 287–93.