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FASTTRACK Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity

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Aims Patients with diabetes have an unfavourable prognosis after an acute myocardial infarction. In the first DIGAMI study, an insulin-based glucose management improved survival. In DIGAMI 2, three treatment strategies were compared: group 1, acute insulin–glucose infusion followed by insulin-based long-term glucose control; group 2, insulin–glucose infusion followed by standard glucose control; and group 3, routine metabolic management according to local practice.

Methods and results DIGAMI 2 recruited 1253 patients (mean age 68 years; 67% males) with type 2 diabetes and suspected acute myocardial infarction randomly assigned to groups 1 ($n = 474$), 2 ($n = 473$), and 3 ($n = 306$). The primary endpoint was all-cause mortality between groups 1 and 2, and a difference was hypothesized as the primary objective. The secondary objective was to compare total mortality between groups 2 and 3, whereas morbidity differences served as tertiary objectives. The median study duration was 2.1 (interquartile range 1.03–3.00) years. At randomization, HbA1c was 7.2, 7.3, and 7.3% in groups 1, 2, and 3, respectively, whereas blood glucose was 12.8, 12.5, and 12.9 mmol/L, respectively. Blood

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glucose was significantly reduced after 24 h in all groups, more in groups 1 and 2 (9.1 and 9.1 mmol/L) receiving insulin–glucose infusion than in group 3 (10.0 mmol/L). Long-term glucose-lowering treatment differed between groups with multidose insulin (≥3 doses/day) given to 15 and 13% of patients in groups 2 and 3, respectively compared with 42% in group 1 at hospital discharge. By the end of follow-up, HbA1c did not differ significantly among groups 1–3 (~6.8%). The corresponding values for fasting blood glucose were 8.0, 8.3, and 8.6 mmol/L. Hence, the target fasting blood glucose for patients in group 1 of 5–7 mmol/L was never reached. The study mortality (groups 1–3 combined) was 18.4%. Mortality between groups 1 (23.4%) and 2 (22.6%; primary endpoint) did not differ significantly (HR 1.03; 95% CI 0.79–1.34; $P = 0.831$), nor did mortality between groups 2 (22.6%) and 3 (19.3%; secondary endpoint) (HR 1.23; CI 0.89–1.69; $P = 0.203$). There were no significant differences in morbidity expressed as non-fatal reinfarctions and strokes among the three groups. **Conclusion** DIGAMI 2 did not support the fact that an acutely introduced, long-term insulin treatment improves survival in type 2 diabetic patients following myocardial infarction when compared with a conventional management at similar levels of glucose control or that insulin-based treatment lowers the number of non-fatal myocardial reinfarctions and strokes. However, an epidemiological analysis confirms that the glucose level is a strong, independent predictor of long-term mortality in this patient category, underlining that glucose control seems to be an important part of their management.

Introduction

Type 2 diabetes is an important cause of cardiovascular morbidity and mortality accounting for >20% of the total number of patients admitted for suspected myocardial infarction. Patients with diabetes have a two-fold increase in hospital mortality when compared with those without diabetes. Long-term follow-up reveals a continuously increasing excess mortality, mostly due to fatal re-infarctions and congestive heart failure.[1–3] The difference in mortality and morbidity between patients with and without diabetes has remained despite improved therapeutic modalities that have resulted in a decline in the overall morbidity and mortality following acute myocardial infarction.[4–6]

Factors of possible importance for the poor prognosis among diabetic patients with acute myocardial infarction may act before, during, or after an event. As recently reviewed, these include diffuse coronary atherosclerosis, a possible diabetic cardiomyopathy, autonomic neuropathy with impaired pain perception and increased heart rate, an increased propensity to thrombus formation, and an impaired fibrinolytic function. Some of these factors are related to the metabolic control and are favourably influenced by insulin.[7] Acute myocardial infarction causes a dramatic increase in adrenergic tone, which stimulates lipolysis, thereby increasing the levels of free fatty acids. Several hormonal mechanisms contribute to a decrease in insulin sensitivity and glucose utilization during acute myocardial ischaemia. This is particularly evident in the diabetic patient, who already has a diminished capability to secrete insulin and to use glucose for production of energy rich phosphates. Free fatty acids are harmful to the myocardium through several mechanisms. In addition, an excessive oxidation of free fatty acids may possibly jeopardize non-ischaemic parts of the myocardium.[8]

In the DIGAMI trial, patients with diabetes and acute myocardial infarction were randomly assigned to a control group or to receive intense insulin treatment initiated by insulin–glucose infusion during the first 24 h after myocardial infarction. The 1 year mortality was reduced by 30% in the intensively treated group. After an average of 3.4 years, there was an 11% absolute mortality reduction among these patients.[9,10] As total mortality in the first DIGAMI study was lower than expected, there was little statistical power to detect reasons for this mortality reduction. Moreover, the study could not answer the question of whether the beneficial effects related to the acute insulin–glucose infusion or to the continuous insulin-based metabolic control or both.

The DIGAMI 2 trial was planned and conducted to further explore the possible benefits of an insulin-based management of diabetic patients with myocardial infarction. The hypothesis behind the study was that early and continued insulin-based metabolic control is a key to mortality reduction.

Methods

Design

DIGAMI 2 was a multicentre, prospective randomized, open trial with blinded evaluation comparing three different management strategies in patients with type 2 diabetes and acute myocardial infarction. The management protocols were (i) a 24 h insulin–glucose infusion followed by a subcutaneous insulin-based long-term glucose control (group 1), (ii) a 24 h insulin–glucose infusion followed by standard glucose control (group 2), and

(iii) routine metabolic management according to local practice (group 3). The study was performed in 44 centres in Sweden, Finland, Norway, Denmark, The Netherlands, and the UK (see Appendix). Patient recruitment started in January 1998 and ended in May 2003. Follow-up for mortality and morbidity was concluded in December 2003.

The primary objective of DIGAMI 2 was to compare total mortality between treatment groups 1 and 2 during the time of follow-up. A secondary objective was to compare the total mortality between groups 2 and 3, and a tertiary objective to compare morbidity, such as non-fatal reinfarction, congestive heart failure, and stroke, among the three groups.

Patients

Patients with established type 2 diabetes or an admission blood glucose >11.0 mmol/L, admitted to participating coronary care units, were eligible for inclusion according to the following criteria: suspect acute myocardial infarction due to symptoms (chest pain >15 min during the preceding 24 h) and/or recent ECG signs (new Q-waves and/or ST-segment deviations in two or more leads). Exclusion criteria were inability to cope with insulin treatment or to receive information on the study; residence outside the hospital catchment area; participation in other studies, or previous participation in DIGAMI 2. The study conformed to good clinical practice guidelines and followed the recommendations of the Helsinki Declaration. Local ethics review boards approved the protocol. Written informed consent was obtained from all patients prior to enrolment.

Procedures

The computer-based randomization was centralized to the study coordinating office open 24 h/day (Karolinska Hospital, Stockholm, Sweden). An attempt for balanced randomization was performed directly after a patient had been evaluated for inclusion, given informed consent, and after baseline variables had been collected. Telecommunicated information about baseline variables were transferred into the computer and the subsequent randomization was based on an algorithm including important prognostic markers in the first DIGAMI trial[9,10] as follows: age (>70 years vs. <70 years); previous myocardial infarction (yes/no); previous congestive heart failure (yes/no); ongoing treatment with digitalis (yes/no). The presence or absence of previous insulin treatment was also taken into account. Besides optimizing the likelihood to obtain comparable study groups, this procedure also improved the possibility to compare the outcome of DIGAMI 2 with predefined risk strata in the first DIGAMI trial.

Concomitant treatment

With regard to the open study design, the protocol stated that the use of concomitant treatment should be as uniform as possible and according to evidence-based international guidelines for acute myocardial infarction.[11,12] In particular, it was emphasized that all patients without contraindications must be prescribed aspirin, thrombolytic agents, beta-blockers, lipid-lowering drugs, angiotensin-converting enzyme (ACE)-inhibitors, and revascularization procedures when appropriate.

Laboratory investigations

Random blood glucose was obtained as soon as possible after hospital admission. During the first 24 h, blood glucose was followed according to the infusion protocol in groups 1 and 2 and at the discretion of the attending physician in charge in group 3. Thereafter, fasting blood glucose was recorded daily until hospital discharge and at each follow-up visit. Data are reported as the locally analysed whole blood glucose in mmol/L. HbA1c was analysed by high-performance liquid chromatography in a core laboratory (Department of Laboratory Medicine, Malmö Hospital, Sweden) on capillary blood applied on filter paper with an upper normal limit of 5.3%. (Boerhringer Mannheim Scandinavian AB, Bromma, Sweden).[13]

Glucose-lowering treatment

In groups 1 and 2, glucose-lowering treatment was initiated with a glucose–insulin infusion as described in detail,[9] with the objective to decrease blood glucose as fast as possible and keep it between 7 and 10 mmol/L. The infusion lasted until stable normoglycemia and at least for 24 h. In group 1, subcutaneous insulin was initiated at the cessation of the infusion. Insulin was given as short-acting insulin before meals and intermediate long-acting insulin in the evening. The treatment goal for patients in group 1 was a fasting blood glucose level of 5–7 mmol/L and a non-fasting level of <10 mmol/L. Apart from the initial insulin–glucose infusion given to patients in group 2, the glucose-lowering treatment in groups 2 and 3 was at the discretion of the responsible physician and according to local routines. The protocol did not define any target values in these groups. Hypoglycaemia was defined as a blood glucose <3.0 mmol/L and was recorded as with or without symptoms.

Follow-up

One week following hospital discharge, patients returned to a nurse-based outpatient clinic, in particular focusing on the treatment of diabetes. Outpatient visits to the responsible physician were scheduled after 3, 6, 9, and 12 months and thereafter every sixth month. All patients were followed for a minimum of 6 months, and the maximum time of follow-up was 3 years.

Events

Myocardial infarction was diagnosed according to the joint recommendations of the ESC and ACC.[14] A reinfarction was defined as a new event >72 h from the index infarction. Stroke was defined as unequivocal signs of focal or global neurological deficit of sudden onset and a duration of >24 h that were judged to be of vascular origin. Deaths were verified with death certificates, hospital records, and explaining letters from the physicians in charge when asked for by the adjudication committee members and autopsy reports when available. Sudden cardiovascular deaths were those that occurred within 24 h following onset of symptoms and without any other obvious reason for the fatal outcome. Deaths were labelled as cardiovascular or non-cardiovascular, and those without any obvious non-cardiovascular cause were considered cardiovascular. Non-cardiovascular deaths, including malignancies, were adjudicated according the same principles as cardiovascular events. An independent committee comprising three experienced cardiologists adjudicated all events blindly and could, as indicated, ask for any type of information felt needed to ensure a correct classification of the events and the reasons for mortality.

Statistical methods

Sample size was based on the 2 year mortality of patients with type 2 diabetes in the control group of the first DIGAMI trial.[10] The estimated 2 year mortality was close to 35% in group 3; however, adjusted to 30% to correct for time-trends in mortality.

It was assumed that the mortality would be lowered to 17% in group 1 and 23% in group 2 corresponding to a mortality reduction of 25% between each of three treatment strategies. These assumptions would require a sample size of 1150 patients in groups 1 and 2 and 700 patients in group 3 for a two-tailed test with an alpha-value of 0.05 and a power of at least 85%. However, the power of a study with similar size as the present is only 50%.

The main analysis was performed by means of an un-adjusted Cox proportional hazards model on an intention to treat basis, while the proportional hazards assumption was not assessed. Adjustment for prognostic variables was applied in a secondary analysis. In an epidemiological analysis, background patient characteristics were entered together with updated values for HbA1c and fasting blood glucose as recorded during the time of follow-up in a Cox time-dependent analysis. For the primary hypothesis, a two-tailed statistical test was used at a 5% significance level, whereas a level of 1% was applied for all other comparisons. SAS version 8:12 was used for all statistical analyses.

The Steering Committee decided to stop patient recruitment on 21 May 2003, with the final follow-up scheduled for 15 December 2003. The reason was slow patient recruitment.

Results

Of 1253 patients, 474 (38%) were allocated to group 1, 473 (38%) to group 2, and 306 (24%) to group 3. The median study duration was 2.1 (interquartile range 1.03–3.00) years. No patient was lost to follow-up. At hospital discharge, 85, 84, and 84% of the patients in groups 1, 2, and 3 fulfilled the diagnosis of myocardial infarction, whereof 44, 42, and 46% were ST-elevation infarctions, respectively. Almost all remaining patients had coronary artery disease mostly presenting as unstable angina pectoris. Newly detected type 2 diabetes, defined as of a duration <1 year, was seen in 21, 24, and 23% of the patients in groups 1, 2, and 3, respectively. Baseline characteristics and pertinent biochemical and clinical data at the time of randomization and after 24 h are presented in *Tables 1* and *2*. The three groups were well balanced in most respects. However, there were significantly fewer previous myocardial infarctions and a trend towards less hypertension and heart failure in group 3. Around one-third had a previous myocardial infarction and the mean diabetes duration was 8 years. Thirty per cent was on some form of insulin treatment before randomization (*Table 1*). HbA1c (mean ≅ 7.3%) and blood glucose (≅12.7 mmol/L) did not differ among the groups at randomization. Blood glucose decreased significantly more in groups 1 and 2 during the first 24 h when compared with group 3, but the absolute difference between these groups and group 3 was only 0.9 mmol/L.

Concomitant treatment during hospitalization and at discharge is outlined in *Table 3*. The use of evidence-based treatment was extensive in all groups. In particular, almost all patients eligible for acute revascularization received such treatment, mostly as thrombolysis. More than 80% of the patients were on beta-blockers at the time of hospital discharge. By the end of the study, somewhat >80% of the patients were on beta-blockers, 80% on aspirin, 65% on ACE-inhibitors/angiotensin receptor blockers (ARB), and 75% on lipid-lowering drugs, without any important differences among the three study groups.

Table 1 Baseline characteristics

Variable	Group 1 ($n = 474$)	Group 2 ($n = 473$)	Group 3 ($n = 306$)	*P*-value
Age [years; mean (SD)]	68.1 (11.4)	68.6 (10.4)	68.4 (11.2)	0.7247
Male gender [*n* (%)]	318 (67.1)	310 (65.5)	209 (68.3)	0.7162
BMI [kg/m^2; mean (SD)]	28.3 (4.9)	28.4 (4.7)	28.4 (4.4)	0.8772
Diabetes duration [years; mean (SD)]	7.9 (8.2)	7.7 (8.3)	8.3 (8.3)	0.6313
Symptom-hospitalization [h; mean (SD)]	4.4 (4.8)	4.5 (4.8)	4.1 (3.8)	0.5758
Symptom-randomization [h; mean (SD)]	12.7 (7.1)	13.5 (7.4)	12.6 (6.8)	0.1583
Previous disease				
Myocardial infarction [*n* (%)]	173 (36.5)	166 (35.1)	84 (27.5)	0.0246
Angina [*n* (%)]	221 (46.6)	220 (46.5)	122 (39.9)	0.1227
Hypertension [*n* (%)]	244 (51.5)	225 (47.7)	138 (45.1)	0.1989
Heart failure [*n* (%)]	89 (18.8)	83 (17.5)	48 (15.7)	0.5415
Current smoker [*n* (%)]	103 (22.0)	124 (26.5)	73 (24.0)	0.2681
Bypass surgery [*n* (%)]	50 (10.5)	57 (12.1)	29 (9.5)	0.5103
Percutanous coronary intervention [*n* (%)]	42 (8.9)	37 (7.8)	21 (6.9)	0.5955
Admission treatment				
Insulin [*n* (%)]	141 (29.7)	154 (32.6)	95 (31.0)	0.6460
Beta-blockers [*n* (%)]	194 (40.9)	201 (42.5)	117 (38.2)	0.4975
Aspirin [*n* (%)]	247 (52.1)	224 (47.4)	153 (50.0)	0.3421
ACE-inhibitor/ARB [*n* (%)]	148 (31.2)	146 (30.9)	96 (31.4)	0.9873
Nitrates [*n* (%)]	127 (26.8)	107 (22.6)	57 (18.6)	0.0286
Lipid lowering [*n* (%)]	134 (28.3)	138 (29.2)	77 (25.2)	0.4597
Calcium antagonists [*n* (%)]	115 (24.3)	119 (25.2)	65 (21.2)	0.4414
Diuretics [*n* (%)]	141 (29.7)	159 (33.6)	96 (31.4)	0.4384
Digoxin [*n* (%)]	35 (7.4)	35 (7.4)	21 (6.9)	0.8210

Table 2 Patient characteristics at randomization and after 24 h

Variable	Group 1 ($n = 474$)	Group 2 ($n = 473$)	Group 3 ($n = 306$)	*P*-value
HbA1c [%; mean (SD)]	7.2 (1.7)	7.3 (1.7)	7.3 (1.7)	0.4806
Blood-glucose at randomization [mmol/L; mean (SD)]	12.8 (4.5)	12.5 (4.4)	12.9 (4.6)	0.4135
Blood-glucose after 24 h [mmol/L; mean (SD)]	9.1 (3.0)	9.1 (2.8)	10.0 (3.6)	0.0001
S-Potassium at randomization [mmol/L; mean (SD)]	4.2 (0.5)	4.1 (0.5)	4.2 (0.5)	0.5483
S-Potassium after 24 h [mmol/L; mean (SD)]	4.1 (0.4)	4.1 (0.5)	4.1 (0.5)	0.3197
S-Creatinine at randomization [mmol/L; mean (SD)]	102 (43)	105 (47)	104 (47)	0.5572
Lipids at randomization				
S-Cholesterol [mmol/L; mean (SD)]	5.1 (1.3)	5.1 (1.3)	5.3 (1.2)	0.3662
S-Triglycerides [mmol/L; mean (SD)]	2.2 (1.7)	2.2 (1.9)	2.2 (2.4)	0.8465
Heart rate [beats/min; mean (SD)]	79 (20)	79 (17)	79 (20)	0.9784
Blood pressure systolic [mmHg; mean (SD)]	136 (25)	132 (24)	137 (27)	0.0213
Blood pressure diastolic [mmHg; mean (SD)]	77 (16)	75 (15)	77 (16)	0.0594
Killip class				0.5091
1 [*n* (%)]	346 (73)	331 (70)	218 (71)	
2 [*n* (%)]	84 (18)	105 (22)	65 (21)	
3 [*n* (%)]	38 (8)	31 (7)	18 (6)	
4 [*n* (%)]	5 (1)	4 (<1)	5 (2)	

Table 3 Treatment in hospital and at discharge

Variables	Group 1 ($n = 474$)	Group 2 ($n = 473$)	Group 3 ($n = 306$)
Acute revascularization	208 (44)	187 (40)	137 (45)
Thrombolysis	171 (36)	160 (34)	116 (38)
Heparin or low weight molecular heparin	368 (78)	382 (81)	224 (73)
At hospital discharge	$n = 450$	$n = 441$	$n = 290$
Beta-blocker	373 (83)	372 (84)	235 (81)
Aspirin	399 (89)	396 (90)	244 (84)
ACE-inhibior/ARB	302 (67)	293 (66)	183 (63)
Calcium antagonist	81 (18)	72 (16)	54 (19)
Ticlopidin/clopidrogel	109 (24)	88 (20)	50 (17)
Diuretic	213 (47)	231 (52)	131 (45)
Lipid lowering	303 (67)	302 (69)	165 (57)
At 2 years	$n = 226$	$n = 227$	$n = 143$
Beta-blocker	191 (85)	195 (86)	112 (78)
Aspirin	191 (85)	181 (80)	119 (83)
ACE-inhibior/ARB	159 (70)	151 (67)	89 (62)
Calcium antagonist	45 (20)	41 (18)	29 (20)
Ticlopidin/clopidrogel	11 (5)	15 (7)	4 (3)
Diuretic	120 (53)	122 (54)	69 (48)
Lipid lowering	173 (77)	169 (74)	102 (71)

Data are presented as *n* (%).

Glucose-lowering treatment and glucose control

The adherence to the infusion protocol was high in groups 1 ($n = 446$; 94%) and 2 ($n = 444$; 94%). Infusion of insulin–glucose was administered to significantly fewer patients in group 3 ($n = 44$; 14%). At the time of hospital discharge, 84, 45, and 39% of the patients in groups 1, 2, and 3 were prescribed insulin at an average dose of 36 (22), 46 (30), and 57 (42) units, respectively. During follow-up, multidose insulin (three or more daily doses) was used in somewhat <50% of the patients in group 1 and in between 15 and 20% in groups 2 and 3, whereas ~10% of the patients in group 1 and ~15–20% of those in groups 2 and 3 did not receive any glucose-lowering drugs. Further details on long-term glucose-lowering treatment are presented in *Table 4*.

Blood glucose <3 mmol/L with and without symptoms was more frequent during the initial 24 h in groups 1 (12.7%; symptomatic 27%) and 2 (9.6%; symptomatic 39%) than in group 3 (1.0%; symptomatic 33%).

Glucose control over time is presented in *Figure 1A* (blood glucose) and *B* (HbA1c). Apart from slightly but statistically significant lower blood glucose after 24 h in groups 1 and 2 compared with group 3, blood glucose and HbA1c did not differ significantly among any of the three groups when comparing the areas under the curve. The levels did not reach the targeted level between 5 and 7 mmol/L in group 1. The average increase in body weight was 4.7 kg in group 1 and 0.4 and 0.2 kg in groups 2 and 3, respectively. Average blood pressure at 2 years of follow-up was 137/77, 139/78, and 139/79 in groups 1, 2, and 3, respectively.

Mortality-intention to treat

Overall, there were 277 deaths in the study (21.3%). Mortality did not differ significantly among the three groups as presented in *Figure 2*. After 2 years of follow-up, the Kaplan–Meier estimated mortality was 23.4% among patients in group 1 when compared with 21.2% in group 2 (HR = 1.03; 95% CI = 0.79–1.34; $P = 0.832$). The corresponding proportion in group 3 was 17.9% (group 1 vs. 3: HR = 1.26, CI = 0.92–1.72; $P = 0.157$). The adjusted HR for the slight imbalance in previous diseases between groups 1 and 3 was 1.19 (CI = 0.86–1.64; $P = 0.29$). Comparing groups 2 and 3, the HR = 1.23 (CI = 0.89–1.69;

Table 4 Glucose-lowering treatment at randomization and at hospital discharge

Glucose-lowering agent	Randomization			Discharge		
	Group 1 ($n = 474$)	Group 2 ($n = 473$)	Group 3 ($n = 306$)	Group 1 ($n = 450$)	Group 2 ($n = 441$)	Group 3 ($n = 290$)
Glibenklamid	119 (25.1)	93 (19.7)	62 (20.3)	19 (4.2)	78 (17.7)	59 (20.3)
Glipizid	32 (6.8)	36 (7.6)	18 (5.9)	7 (1.6)	31 (7.0)	21 (7.2)
Glimeperid	22 (4.6)	25 (5.3)	9 (2.9)	7 (1.6)	30 (6.8)	17 (5.9)
Metformin	116 (24.5)	118 (24.9)	75 (24.5)	26 (5.8)	110 (24.9)	64 (22.1)
Acarbose	2 (0.4)	5 (1.1)	5 (1.6)	0 (0.0)	5 (1.1)	4 (1.4)
Not on any oral drug	227 (47.9)	238 (50.3)	163 (53.3)	397 (88.2)	211 (47.8)	137 (47.2)
Insulin						
Once-daily	32 (6.8)	32 (6.8)	17 (5.6)	40 (8.9)	36 (8.2)	22 (7.6)
Twice-daily	64 (13.5)	77 (16.3)	45 (14.7)	151 (33.6)	93 (21.1)	52 (17.9)
Multiple doses	45 (9.5)	45 (9.5)	33 (10.8)	191 (42.4)	67 (15.2)	38 (13.1)
Not on any treatment	131 (27.6)	138 (29.2)	107 (35.0)	42 (9.3)	73 (16.6)	61 (21.0)

Data are presented as n (%).

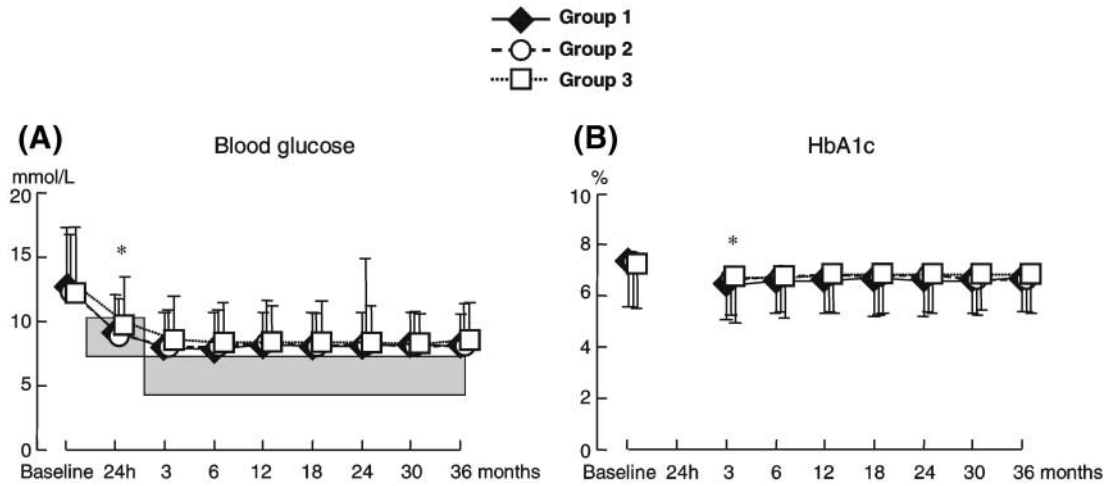

Figure 1 Glucose control expressed as fasting blood glucose (*A*) and HbA1c (*B*). The grey area (*A*) represents the target levels for blood glucose.

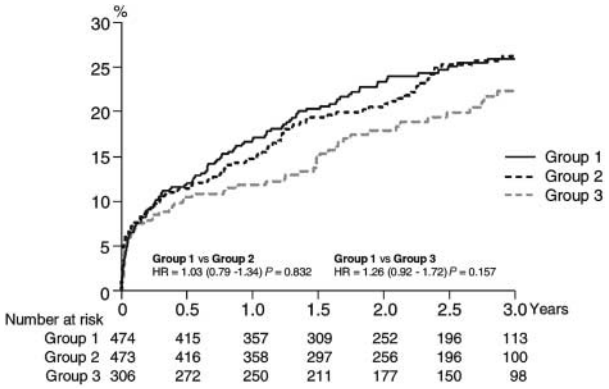

Figure 2 Mortality in groups 1, 2, and 3 (intention to treat analysis).

$P = 0.203$). The following variables were selected for the adjusted endpoint analysis owing to their univariate relation with a P-value < 0.20: myocardial infarction, chronic congestive heart failure, early ventricular fibrillation, and cardiogenic shock. Gender did not influence mortality. Specific causes of death are outlined in *Table 5*. Cardiovascular causes were most common without any significant differences among the groups, whereas a lower incidence of non-cardiovascular deaths in group 3 explained the trend towards a somewhat lower overall mortality in this group compared with groups 2 and 3. There was a slight difference in mortality from malignancies, with a higher incidence in group 1 ($n = 16$) compared with group 2 ($n = 5$) and group 3 ($n = 2$; group 1 vs. 2, $P = 0.016$; group 1 vs. 3, $P = 0.011$). Eleven out of the 16 deaths due to malignancies in group 1 occurred during the first year of follow-up but none in groups 2 and 3, in which the first death due to malignant disease occurred after 1.2 and 1.9 years, respectively.

Mortality—epidemiological analysis

Disregarding group allocation, entering patients characteristics, which in a univariate relation had a

Table 5 Specific causes of death

Cause of death	Group 1 ($n = 474$)	Group 2 ($n = 473$)	Group 3 ($n = 306$)
Cardiovascular*	87 (18.4)	93 (19.7)	53 (17.3)
Index infarction	18 (3.8)	21 (4.4)	13 (4.2)
Reinfarction	25 (5.2)	26 (5.5)	10 (3.2)
Sudden cardiovascular	27 (5.7)	26 (5.5)	16 (5.2)
Stroke	6 (1.3)	6 (1.3)	2 (0.7)
Congestive heart failure	4 (0.8)	13 (2.7)	8 (2.6)
Other cardiovascular	7 (1.5)	1 (0.2)	4 (1.3)
Non-cardiovascular†	24 (5.4)	14 (3.0)	6 (2.0)
Malignancies‡	16 (3.4)	5 (1.1)	2 (0.7)
Other (infection, complications)¶	8 (1.7)	10 (1.9)	4 (1.3)

Data are presented as *n* (%).
*Group 1 vs. group 2, $P = 0.609$; group 1 vs. group 3, $P = 0.623$; group 2 vs. group 3, $P = 0.330$.
†Group 1 vs. group 2, $P = 0.105$; group 1 vs. group 3, $P = 0.021$; group 2 vs. group 3, $P = 0.301$.
‡Group 1 vs. group 2, $P = 0.016$; group 1 vs. group 3, $P = 0.011$; group 2 vs. group 3, $P = 0.471$.
¶Group 1 vs. group 2, $P = 0.624$; group 1 vs. group 3, $P = 0.602$; group 2 vs. group 3, $P = 0.320$.

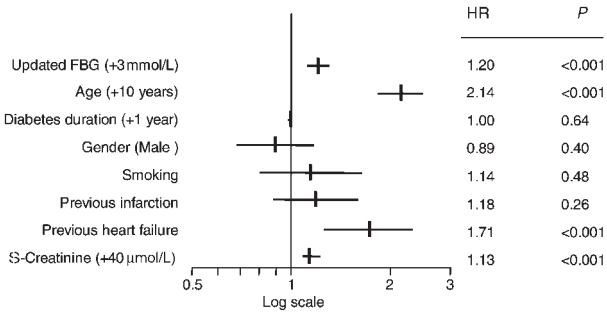

Figure 3 Independent baseline predictors for mortality. Fasting blood glucose represents updated values during the time of follow-up.

P-value < 0.20 [updated mean HbA1c or updated mean blood glucose (depending on the analysis) together with age, gender, diabetes duration, previous heart failure, previous myocardial infarction, smoking, renal function expressed as s-creatinine at the time of randomization] into a multivariable analysis of mortality predictors (*Figure 3*). Updated blood glucose (HR = 1.20 for 3 mmol/L; $P < 0.001$) was a significant and independent predictor together with increasing age (HR = 2.14 for 10 years; $P < 0.001$), previous heart failure (HR = 1.71; $P < 0.001$), and elevated serum creatinin (HR = 1.13 for 40 μmol/L; $P < 0.001$). Applying this model introducing a 2% increase of updated HbA1c as a measure of glucose control revealed an HR of 1.19 ($P = 0.027$).

Morbidity

There was a trend towards fewer secondary events in groups 2 and 3 compared with group 1. However, this difference as presented in *Figure 4* did not reach statistical significance for stroke (*A*) or myocardial reinfarction (*B*). Time to first major event (death, stroke, or reinfarction) has been outlined in *Figure 5*. The combined total event rate was high in the magnitude of 35–40%, but did not differ significantly among the three groups.

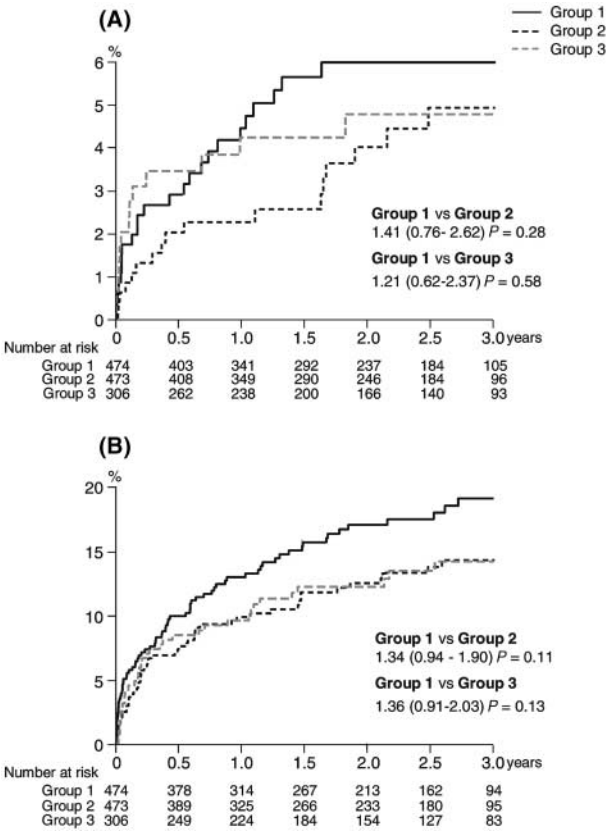

Figure 4 Time to the secondary endpoints stroke (*A*) and myocardial reinfarction (*B*).

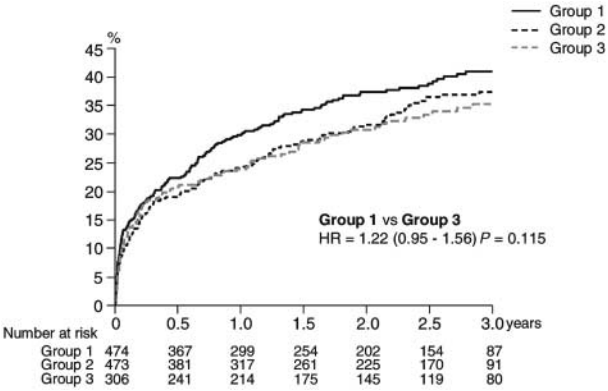

Figure 5 Time to first major event (death, reinfarction, or stroke).

Discussion

The most important message from this investigation of three different treatment strategies for glucose control in patients with type 2 diabetes and acute myocardial

infarction is that they were similar with regard to effects on long- or short-term mortality. Still, hyperglycaemia remained one of the most important prognostic predictors.

The DIGAMI 2 study, originally planned to recruit 3000 patients, was stopped prematurely owing to the slow patient recruitment rate. The slow recruitment may seem surprising in that diabetic patients comprise at least 20–25% of patients with myocardial infarction.[3,15] An obvious solution would have been to increase the number of study centres and such attempts were repeatedly made. The nature of the study, a truly investigator-initiated trial, rendered it a low-budget trial despite generous research grants. A common reason for invited centres to decline participation was that the reimbursement offered was considered too low as it was based on calculations of actual resource consumption. This experience raises the question of whether time has come to discuss for which trials community-owned hospitals should be open, as well as reimbursement possibilities and principles in future clinical research, as has been acknowledged by the European Society of Cardiology.[16]

The slow recruitment rate and the fact that some centres recruited relatively few patients explained the slight imbalance among the three groups because the randomization algorithm was not applied until eight patients were included in an individual centre. This caused the patients in group 3 to be somewhat less sick than those in groups 2 and 3. Comparisons among groups were accordingly done both for crude and for adjusted HRs.

The Steering Committee repeatedly emphasized the importance of a strict adherence to the set targets for glucose control in study group 1. The protocol stated that patients in groups 2 and 3 should be treated at the discretion of the attending physician. The adherence to the glucose–insulin infusion prescribed for patients in groups 1 and 2 was high. This resulted in a better glucose control during the hospital period in these two groups than among those in group 3. However, although statistically significant, this difference was smaller than expected. Importantly, a total of 14% of patients in group 3 received insulin–glucose infusion, which was not advocated by the protocol, and as many as 41% had extra insulin injections. In contrast, the continued glucose-lowering treatment in group 1 was less effective than prescribed by the protocol. Many more patients in group 1 were on insulin than in groups 2 and 3, but $<$50% received insulin three or more times per day. It is therefore not surprising that long-term glucose control did not differ significantly among the three groups. It had been postulated that insulin-based treatment should be superior to glucose-lowering therapy by means of oral glucose-lowering agents. Thus, it was considered important to recruit enough patients to address this hypothesis. The reason for the somewhat vague conclusion in this respect is that the power of the study was decreased to $\sim$50% owing to the lower than planned number of recruited patients. Considering the very small differences in mortality among the three management strategies, it is still not reasonable to assume that a larger patient material would have disclosed any clinically meaningful differences between the different glucose-lowering treatments. Thus, the interpretation must be that there is no evidence to support a beneficial effect of insulin if sufficient amounts are not given to achieve a difference in glucose levels. The targeted level for glucose control in group 1, fasting blood glucose of 5–7 mmol/L, is in agreement with recent guidelines for prevention in patients with cardiovascular disease.[17] The experience from DIGAMI 2, conducted by investigators with a special interest in the care of diabetic patients with acute myocardial infarction, indicates that this goal may be difficult to accomplish. Despite a strict protocol-defined strategy, in particular for patients in group 1, the target was not reached. Experience from the CODE study[18] and registries[19] does indeed support the finding that glucose control often is far from satisfactory albeit slowly improving.[20] Accordingly, other management routines, including forced titration algorithms and improved pharmacological agents, are warranted for this large group of patients.

The outcome of DIGAMI 2 contrasts with the findings in the first DIGAMI trial, which concluded that an insulin–glucose infusion followed by insulin-based therapeutic regime reduced mortality in diabetic patients with acute myocardial infarction.[9,10] Although the design of the second DIGAMI trial was based upon the first, there are differences. DIGAMI 1 recruited patients with any type of diabetes and required a blood glucose $>$11.0 mmol/L for eligibility, whereas the present patient population consisted of patients with type 2 diabetes without any blood glucose restrictions. This is demonstrated by the higher baseline blood glucose (15.5 ± 4.5 vs. 12.8 ± 4.5 mmol/L) in DIGAMI 1 when compared with DIGAMI 2. The reason for this is probably not only different eligibility criteria, but also an overall improved glycaemic control in diabetic patients.[19] In addition, the initial decrease in blood glucose was more substantial in DIGAMI 1 (-5.8 mmol/L) than in DIGAMI 2 (-3.4 mmol/L), which may reflect that it was felt safer to lower a high glucose level than to normalize a lower value with an experienced risk of causing hypoglycaemia. Considering long-term glucose control, the insulin-based management strategy reduced HbA1c by 1.4% in the subgroup that benefited most in DIGAMI 1 which should be compared with 0.5% in all groups in DIGAMI 2. The overall long-term glucose control was better in the second than in the first DIGAMI trial, which may have had a favourable influence on the outcome in the latter. In DIGAMI 1, glucose control differed clearly between the insulin-treated and the control arms, but such difference was unfortunately not achieved in DIGAMI 2. The most likely reasons for this discrepancy are a better-than-expected blood glucose control in groups 2 and 3 in DIGAMI 2 and a less-than-ideal adherence to the use of insulin. The interpretation of DIGAMI 2 is that for a similar glycaemic control insulin treatment is not superior to the use of other therapeutic options as regards mortality outcome. DIGAMI 2 could

not provide a firm answer to the important question of whether a glucose-lowering treatment towards normoglycaemia has a potential to further improve prognosis. The epidemiological analysis from DIGAMI 2 together with information from the study on patients in intensive care by Van den Berghe *et al.*[21] strongly support the concept that a meticulous glucose control rather than insulin treatment or the insulin dose[22] is the important factor. Thus, DIGAMI 2 supported by previous data suggests that type 2 diabetic patients should have an intensive glucose control after an acute myocardial infarction, but that this may be accomplished by alternative and perhaps more convenient treatment than insulin as long as glucose control is efficient.

The concept of initiating treatment with insulin infusion to rapidly attain a normalized blood glucose has support from the first DIGAMI trial and the study in patients in intensive care by Van den Berghe *et al.*[21] DIGAMI 2 does not provide evidence against such therapy in patients with high admission blood glucose, but a pre-requisite seems to be that glucose is monitored carefully to achieve effective control. Other studies more directed towards metabolic support to the ischaemic myocardium are not comparable. None of them aimed for glucose control as a primary target. Indeed blood glucose increased in most of these studies during infusion of high concentrations of glucose–insulin–potassium.[23,24]

Mortality remains high among patients with diabetes and myocardial infarction as shown by recent registry studies, also reporting on a suboptimal use of established treatment modalities in these patients.[3,25,26] In contrast, the overall mortality in DIGAMI 2 was considerably lower than the predicted 2-year mortality of 22–23%, which was based on the outcome of the first DIGAMI study with corrections for assumed time-trend in mortality owing to improved general management. A concern was a higher death rate by malignancies in group 1 than in groups 2 and 3. In group 1, most of these deaths occurred early, during the first year of follow-up, which is strong evidence against a true relation. The most likely explanation is unfavourable patient allocation in this particular respect, not covered for by our attempt to cause a balanced randomization. Moreover, the question concerning a possible relation between insulin and malignant diseases cannot be based on the few events in this trial but should, if of any further interest, be studied in large databases.

The actual 2 year mortality of 18.4% is, to the best of our knowledge, the lowest presented long-term mortality in a cohort of diabetic patients with myocardial infarction. This becomes even more evident when comparing the present 1-year mortality (≈14%) with updated information on diabetic patients in the Swedish CCU registry (21%; data on file). Indeed, the 1-year mortality in DIGAMI 2 approaches ∼12% that for the non-diabetic registry patients. Needless to say, a selection bias hampers such comparisons, but the inclusion criteria in the DIGAMI 2 were wide and without age limits, whereas the registry does not include people above the age of 80 years. Although firm conclusions cannot be based on such comparisons, the DIGAMI 2 findings are promising. The most likely reasons for this beneficial outcome are a combination of improved glucose control and an extensive use of evidence-based treatment as prescribed by the protocol. Despite the fact that patients in study group 1 did not reach the protocol-outlined glucose levels, patients in all study groups alike had a better long-term glucose control than those in the first DIGAMI study. As regards concomitant treatment, thrombolysis or revascularization procedures were in principle offered to all patients with ST-elevation infarctions, and the use of beta-blockers, ACE-inhibitors, lipid-lowering drugs, and aspirin were indeed high. This assumption is supported by short-term data from the Munich registry report that intensification of multiple therapeutic strategies, including insulin infusions, resulted in a substantial reduction of in-hospital mortality comparable to the rates in non-diabetic patients.[27]

An important message from the DIGAMI 2 trial is that updated HbA1c and blood glucose were significant and independent mortality predictors together with the traditional risk factors age, heart failure, and elevated serum creatinin. Thus, an increase in blood glucose of 3 mmol/L or in HbA1c by 2% was associated with an increase in mortality by 20%. This underlines the importance of efforts finding pharmaceutical agents and management strategies that can effectively normalize blood glucose levels.

Conclusions

The DIGAMI 2 trial did not support that an acutely introduced, long-term insulin treatment improves survival in type 2 diabetic patients following myocardial infarction compared with a conventional management at similar levels of glucose control or that insulin-based treatment lowers the number of non-fatal myocardial reinfarctions and strokes. However, an epidemiological analysis confirms that the glucose level is a strong, independent predictor of long-term mortality in this patient category, underlining that glucose control is an important part of their management.

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