The Hyperglycemia: Intensive Insulin Infusion In Infarction (HI-5) Study

A randomized controlled trial of insulin infusion therapy for myocardial infarction

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OBJECTIVE — There is conflicting evidence regarding the benefit of intravenous insulin therapy on mortality following acute myocardial infarction (AMI). The goal of the current study was to determine whether improved glycemic control, achieved through an insulin/dextrose infusion with a variable rate of insulin, reduces mortality among hyperglycemic patients with AMI.

RESEARCH DESIGN AND METHODS — Subjects suffering AMI with either known diabetes or without diabetes but blood glucose level (BGL) ≥7.8 mmol/l were randomized to receive insulin/dextrose infusion therapy for at least 24 h to maintain a BGL <10 mmol/l or conventional therapy.

RESULTS — A total of 240 subjects were recruited. Insulin/dextrose infusion did not reduce mortality at the inpatient stage (4.8 vs. conventional 3.5%, $P = 0.75$), 3 months (7.1 vs 4.4%, $P = 0.42$), or 6 months (7.9 vs. 6.1%, $P = 0.62$). There was, however, a lower incidence of cardiac failure (12.7 vs. 22.8%, $P = 0.04$) and reinfarction within 3 months (2.4 vs. 6.1%, $P = 0.05$). When analyzed by mean BGL achieved during the first 24 h, mortality was lower among subjects with a mean BGL ≤8 mmol/l, compared with subjects with a mean BGL >8 mmol/l (2 vs. 11% at 6 months, $P = 0.02$).

CONCLUSIONS — We did not find a reduction in mortality among patients who received insulin/dextrose infusion therapy. However, it remains possible that tight glycemic control with insulin therapy following AMI improves outcomes.

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There has been interest in the possibility that insulin administration would improve outcomes of acute myocardial infarction (AMI). In the 1990s, this was supported by two large clinical trials (1,2) and a meta-analysis of earlier smaller clinical trials (3). However, two recent larger trials (4,5) failed to demonstrate reduced mortality from insulin-based therapy in AMI.

The studies of insulin infusion therapy for AMI can be divided into two categories according to their treatment goal: either the delivery of insulin (insulin focus) or the control of hyperglycemia (glycemia focus). The Estudios Cardiologicos Latinoamerica (ECLA) (2), Clinical Trial of Revirapine and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation (CREATE)–ECLA (5), Pol–glucose-insulin-potassium (GIK) (6), and Dutch GIK (7) studies are examples of the former. These studies used GIK in fixed proportions to deliver a large dose of insulin. The insulin is administered without particular regard to glucose levels.

In contrast, the Diabetes Insulin-Glucose infusion in Acute Myocardial Infarction (DIGAMI) (1) and DIGAMI-2 (4) studies had a glycemia focus and aimed to achieve normoglycemia. In the DIGAMI study, glucose control with insulin therapy decreased the 1-year mortality among hyperglycemic patients admitted to hospital with AMI by 29% (1). Unfortunately, the subsequent DIGAMI-2 study failed to replicate this result (4). However, the insulin-treated patients in DIGAMI-2 did not achieve the glucose targets of the study protocol. It can therefore be argued that the benefit of tight glycemic control following AMI has not been fully tested.

Like the DIGAMI studies, the goal of the Hyperglycemia: Intensive Insulin Infusion In Infarction (HI-5) study was to determine whether tight glycemic control improves outcomes for hyperglycemic patients with AMI. Glucose control was to be achieved through an insulin/dextrose infusion with a variable rate of insulin. However, our study design limited the intervention to the immediate postinfarct period, thereby testing the effect of periinfarct glucose control, without the confounding factor of altered long-term glycemic control. Furthermore, we planned to collect detailed information regarding glycemic control during the insulin infusion to enable a closer examination of the effect of glucose control on outcomes.

RESEARCH DESIGN AND METHODS

— The HI-5 study was a multicenter open-label randomized controlled clinical trial conducted at six hospitals in the state of New South Wales, Australia. It commenced in 2001 and re-

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Abbreviations: AMI, acute myocardial infarction; BGL, blood glucose level; CPK, creatinine phosphokinase; CREATE, Clinical Trial of Revirapine and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation; CTG, conventional therapy group; DIGAMI, Diabetes Insulin-Glucose infusion in Acute Myocardial Infarction; ECLA, Estudios Cardiologicos Latinoamerica; GIK, glucose-insulin-potassium; HI-5, Hyperglycemia: Intensive Insulin Infusion In Infarction; ITG, intensive insulin infusion therapy group; PTCA, percutaneous angioplasty.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

cruitment occurred over 3.5 years. Approval was obtained from all local ethics committees. The study conformed with good clinical practice guidelines and the recommendations of the Declaration of Helsinki.

The eligibility criteria for the HI-5 Study were *1*) evidence of AMI within the last 24 h (troponin-T >0.1 μg/l or electrographic criteria of ST-segment elevation in two limb leads) and *2*) known diabetes or not diabetic with an admission blood glucose level (BGL) ≥7.8 mmol/l (140 mg/dl). Exclusion criteria included pregnancy, diabetic ketoacidosis, and admission BGL ≥20 mmol/l.

Randomization

Consenting eligible subjects were randomized to either the intensive insulin infusion therapy group (ITG) or the conventional therapy group (CTG). Randomization was stratified into stratification 1 (known diabetes or admission BGL ≥11.1 mmol/l without known diabetes) or stratification 2 (admission BGL 7.8–11 mmol/l without known diabetes). This was designed to ensure an even distribution of subjects with different degrees of hyperglycemia. Predetermined subanalyses were planned to examine subjects by stratification and diabetes status.

Randomization was conducted in randomly computer-generated blocks of 20. As randomization calls were received, eligibility criteria would be assessed and the subject allocated the next designated group within the appropriate stratification.

ITG

Subjects allocated to ITG were placed on insulin at 2 units/h and 5% dextrose at 80 ml/h. Insulin was titrated according to an algorithm to maintain the BGL between 4 and 10 mmol/l (72–180 mg/dl) for at least 24 h. This level of glycemic control was chosen to concord with the upper glucose target in the DIGAMI study (1). Dextrose was included in the protocol as it was a component of our standard hospital insulin infusion regimen. This facilitated its implementation, as the trial relied on a large number of staff, many of whom did not receive specific training in the study protocol.

For patients with cardiac failure, 10% dextrose was administered at 40 ml/h. Insulin was not adjusted for meals, except in response to changes in BGL. All diabetes medications were discontinued temporarily. Upon cessation of insulin/dextrose infusion, patients resumed their usual diabetes medications, but metformin was recommenced only when appropriate.

CTG

Those in CTG remained on their usual diabetes therapy (including subcutaneous insulin), but metformin was temporarily discontinued. Supplemental subcutaneous short-acting insulin was permitted if the BGL exceeded 16 mmol/l.

Assessment of glycemic control

Capillary glucose levels were measured at eight predefined time points by fingerprick testing for the first 24 h to determine a mean 24-h BGL. These were at 0700, 0900, 1200, 1400, 1700, 1900, 2200, and 0300, with the first six corresponding to before and after meals. Additionally, ITG patients had hourly monitoring of BGL during the day and second hourly overnight. HbA_{1c} (A1C) was assessed on randomization and, for subjects with diabetes, repeated after 3 and 6 months.

Cardiac care

All subjects underwent standard cardiology care. Percutaneous angioplasty (PTCA) and thrombolysis therapy took precedence and therefore occurred before insulin was commenced. In general, PTCA with stenting was performed for patients under 75 years of age, with ST-segment elevation myocardial infarction within 4 h of pain onset. Otherwise, patients with ST-segment elevation myocardial infarction were administered thrombolytic therapy (streptokinase or tissue plasminogen activator) if they presented within 12 h. Heparin infusion or subcutaneous low–molecular weight heparin was commenced at the discretion of the cardiologist. All patients were given standard antiplatelet therapy, statins, and β-blockade unless contraindicated. Serial creatinine phosphokinase (CPK) and potassium levels were measured every 6–8 h during the first 24 h.

Subsequent management

Patients with diabetes were managed in the standard manner by their own physician after the cessation of the insulin/dextrose infusion for those in the ITG and after 24 h for those in CTG. The study team did not intervene in diabetes management, although it was recommended that the A1C be maintained at <7% for all patients.

Follow-up

Subjects were contacted to obtain information regarding the occurrence of cardiovascular events following discharge. If the subject was not contactable, the next of kin and/or the subject's general practitioner would be contacted. Where no information could be obtained, a request was made to the Department of Births, Deaths, and Marriages to ascertain whether the patient was deceased.

Outcomes

The primary outcome of the study was patient mortality during the index hospital admission and after 3 and 6 months, analyzed on an intention-to-treat basis. Secondary outcomes were the development of major cardiac events and a composite end point comprising death or any major cardiac event. The major cardiac events were reinfarction, defined as new AMI occurring >72 h following the index infarct; cardiac failure, defined as dyspnoea with radiographic evidence of pulmonary or interstitial edema; and cardiogenic shock, defined as cardiac failure with a systolic blood pressure <80 mmHg. Hypoglycemia referred to a fingerprick BGL <3.5 mmol/l, irrespective of the occurrence of symptoms.

Sample size estimation

Sample size estimations were based on published data available at the time (1,8,9). Applying a modest base mortality rate of 25% at 1 year and equal distribution of patients in each group, 850 subjects were needed to achieve 80% power at $P < 0.05$ to detect a 30% reduction in mortality. Based on hospital audit data, we expected that this number could be recruited within 2.5 years.

Recruitment was terminated in 2004, as numbers were below expectations and a preliminary examination of the data did not suggest a survival benefit of intensive therapy. It was judged by the steering committee that a reasonable extension of recruitment time was unlikely to significantly alter the results.

Statistics

Statistical analysis was conducted with the program SPSS. Categorical variables were compared by χ^2 analysis. Continuous variables were examined by ANOVA. Comparison of nonparametric variables was by the Mann-Whitney *U* test. Relationships between variables were examined by logistic regression. Multiple logistic regression was used to conduct

Table 1—*Baseline subject characteristics*

	Intensive group	Conventional group	*P* value
n	126	114	
Age	61.9 ± 11.4	63.4 ± 11.2	0.33
Male	100 (79)	88 (77)	0.68
Known diabetes	64 (51)	52 (46)	0.42
Stratification 1	73 (58)	69 (61)	0.79
Known ischaemic heart disease	42 (33)	43 (38)	0.50
Known hypertension	67 (53)	68 (60)	0.41
Known hyperlipidemia	68 (54)	67 (59)	0.48
Current smoker	39 (31)	37 (32)	0.84
Cardiac treatment			
Aspirin	37 (29)	23 (20)	0.09
β-Blockers	20 (16)	17 (15)	0.82
ACE inhibitor/A2RB	24 (24)	19 (17)	0.61
Nitrates	18 (14)	13 (11)	0.49
Statin	38 (30)	32 (28)	0.73
Fibrate	1 (1)	1 (1)	0.94
Diabetes treatment			
Insulin	15 (12)	14 (12)	0.97
Metformin	36 (29)	26 (23)	0.16
Sulphonylureas	29 (23)	22 (19)	0.33
Baseline BGL	10.8 ± 4.1	11.1 ± 3.5	0.23
A1C	7.0 ± 1.7	7.0 ± 1.7	0.87
Infarct type			
Anterior/anteroseptal	41 (33)	32 (28)	0.43
Inferior	48 (38)	54 (47)	
Non–ST-segment elevation myocardial infarction	34 (27)	24 (21)	
Not classified	3 (2)	4 (4)	
Cardiac intervention			
PTCA	40 (32)	45 (39)	0.37
Thrombolysis	40 (32)	36 (32)	
No reperfusion	46 (37)	33 (29)	
Heparin or low–molecular weight heparin	61 (48)	50 (44)	0.41

Data are *n* (%) or means ± SD, unless otherwise indicated.

multivariate analyses and calculation of adjusted risk. Data are presented as means ± SD.

RESULTS — There were 244 subjects randomized into the study. Two subjects were found to be ineligible and two withdrew consent immediately following randomization, leaving 240 subjects, 188 men and 52 women. There were 126 randomized to the ITG and 114 to the CTG, with no differences in baseline characteristics (Table 1). The mean age was 63 ± 11 years, and 116 subjects had known diabetes (all type 2). The BGL at admission was 11.0 ± 3.8 mmol/l. There were 142 subjects in stratification 1 and 98 in stratification 2.

The baseline BGL was 10.8 ± 4.1 mmol/l in the ITG and 11.1 ± 3.5 mmol/l in the CTG (NS). The mean 24-h BGL was 8.3 ± 2.2 and 9.0 ± 2.8 mmol/l, respectively (NS). The mean insulin dose administered over this time in the ITG was 46 ± 30 units, equivalent to 1.9 units/h. The time from symptom onset to commencement of insulin was 13.2 ± 8.4 h. In the ITG, 93% of patients received an insulin infusion for at least 24 h, with a mean duration of 31 ± 22 h. Fifteen patients in the conventional group received supplemental subcutaneous insulin injections. There was no difference in A1C at 3 (6.9 ± 1.2 vs. 6.8 ± 1.1%, NS) and 6 (7.4 ± 1.2 vs. 7.0 ± 1.0%, NS) months among subjects with diabetes. Follow-up at 6 months was successful for 94% of subjects.

Overall outcomes

The overall inpatient mortality was 4.2% and at 6 months, 7.1%. There was no difference in mortality between the groups at the inpatient stage (ITG 4.8%, CTG 3.5%, $P = 0.75$), 3 months (7.1 vs. 4.4%, $P = 0.42$), or 6 months (7.9 vs. 6.1%, $P = 0.62$). There was a lower incidence of cardiac failure during the inpatient period (12.7 vs. 22.8%, $P = 0.04$) and of reinfarction within 3 months (2.4 vs. 6.1%, $P = 0.05$) in the ITG. There were no other differences in any of the secondary cardiac outcomes or in the occurrence of composite end points.

Subgroup analyses

Subgroup analyses by stratification and diabetes status demonstrated no differences in mortality at any stage. Among subjects with diabetes, there was a lower reinfarction rate in the ITG (0 vs. 7.7%, $P = 0.04$) and a lower occurrence of composite end points (21.9 vs. 40.4%, $P = 0.03$) at 3 months. There were no differences in the other outcome variables. Among subjects without diabetes, there was a lower incidence of cardiac failure in the ITG during the inpatient period (11.3 vs. 27.4%, $P = 0.02$). There were no differences in other outcome variables.

Glucose control and mortality

We also analyzed outcomes according to level of glycemic control achieved in the first 24 h following randomization. These data were collected for 97.5% of subjects. The mean 24-h BGL was associated with risk of death in hospital ($P = 0.03$) and borderline at 6 months ($P = 0.06$). As the mean 24-h BGL was distributed around a median level of 8.1 mmol/l (144 mg/dl), we divided the overall cohort into two groups, ≤8 and ≥8.1 mmol/l, for further analysis. There were no significant differences between these two groups in age, sex, history of ischemic heart disease, hypertension, hyperlipidemia, smoking, cardiac medication, infarct type, and heparin use. However, subjects with a mean BGL ≤8 mmol/l were more likely to have undergone PTCA (57 vs. 43%, $P = 0.007$). The mortality among subjects with a mean 24-h BGL ≥8.1 mmol/l was higher than those with mean 24-h BGL ≤8 mmol/l, even after adjustment for cardiac intervention (PTCA and thrombolysis), as well as age and sex (Table 2). The peak CPK was not higher in the group with mean 24-h BGL ≥8 mmol/l, with a trend in the opposite direction (median 880 vs. 1,200 mmol/l, $P = 0.06$). There was no relationship between the baseline BGL or insulin dose with mortality.

Table 2—*Mortality when cohort divided into those with a mean glucose level in first 24 h above and below 8 mmol/l.*

	24-h mean blood glucose level ≤8 mmol/l	24-h mean blood glucose level ≥8.1 mmol/l	Significance	Adjusted odds ratio (95% CI)*	*P*
Inpatient mortality	0%	7%	0.05	7.2 (0.9–58.9)	0.07
3-month mortality	2%	9%	0.05	4.7 (1.0–22.4)	0.05
6-month mortality	2%	11%	0.02	5.6 (1.2–26.1)	0.03

*Adjusted for age, sex, and cardiac intervention (PTCA or thrombolysis).

Adverse effects

There were 13 episodes of hypoglycemia among the ITG and 2 episodes in the CTG ($P = 0.02$). No patient developed significant symptoms. There was no difference in the trough potassium level between the two groups (3.8 ± 0.0 vs. 3.9 ± 0.1 mmol/l, $P = 0.11$). The lowest serum potassium level was 2.9 mmol/l in two patients, with one each from each group.

CONCLUSIONS — In the HI-5 study, a variable-rate insulin infusion protocol aimed at controlling hyperglycemia did not reduce short-term mortality following AMI using an intention-to-treat analysis. Our findings are similar to those of the recently reported CREATE-ECLA (5) and DIGAMI-2 (4) trials but contrast with earlier studies in which a survival advantage was demonstrated in insulin-treated patients (1,2).

There are a number of factors that may have contributed to the lack of effect of insulin therapy on mortality in the HI-5 study. In the HI-5 study, the usual cardiac therapies took priority over the commencement of insulin therapy. Consequently, the mean duration of symptom onset to commencement of insulin was 13 h. As this approximates the time of peak CPK levels, insulin may have been commenced too late for significant myocardial salvage, reducing the potential for an immediate impact. While the DIGAMI (1,4) studies and the Dutch GIK trial (7) also accepted patients up to 24 h after symptom onset, it is possible that earlier initiation of insulin, and earlier control of hyperglycemia, would have be more effective. There is also evidence that insulin given before reperfusion therapy is beneficial, possibly by reducing reperfusion injury (7). By administering reperfusion therapy first we lost this potential benefit. Finally, the overall inpatient and 6-month mortality rate of 4.6 and 7.1%, respectively, in this cohort was lower than expected. This compares with an inpatient mortality of 11.4% for AMI at our core institution in 2000 (10). This resulted in loss of power to detect an effect of insulin but also suggests that other changes in management such as the wider use of statin, β-blocker, aspirin, and PTCA therapy may have outweighed any benefit of insulin treatment.

Another likely major contributory reason for the negative result of the HI-5 study is that a significant difference in BGL between treatment and control groups was not achieved. Similarly, glucose targets were not achieved in DIGAMI-2 (4), although insulin-treated subjects had a lower fasting BGL after 24 h (9.1 vs. 10 mmol/l). It is evident that despite a glycemia focus, strict control of blood glucose in patients with AMI is difficult to attain. However, the detailed record of patients' BGL during insulin infusion enabled analysis according to actual BGL achieved in the 24 h after entry into the study, rather than treatment allocation. Tight glycemic control (mean glucose ≤8 mmol/l) in the immediate postinfarct period was associated with lower mortality, regardless of whether insulin was given. This agrees with data from observational studies correlating elevated BGL with poor outcome in AMI (8–11) and other critical illnesses (12,13). In the CREATE-ECLA study, analysis of the cohort according to admission BGL found that the mortality rate increased from 6.6 to 8.5 and 14% in the lowest, middle, and highest tertiles, respectively. However, because of the small numbers and lack of a demonstrable effect of insulin therapy on an intention-to-treat analysis in the HI-5 study, firm conclusions regarding the merits of routine insulin infusion therapy to control BGL cannot be drawn. Moreover, it is possible that an elevated BGL is simply a marker of more severe illness, although patients with a BGL >8 mmol/l in the HI-5 study did not have higher peak CPK levels, suggesting that their infarct size was no greater than for those subjects with a BGL ≤8 mmol/l.

There is other evidence, however, that insulin therapy with a glycemia focus, aiming for tight glucose control in AMI and critical illness, improves survival. An early study using historical control subjects found that the implementation of insulin infusion to maintain the BGL between 4 and 7 mmol/l reduced mortality from 42 to 17% (14). In the DIGAMI study there was a reduction of 1-year mortality by 29% when peri-infarct blood glucose levels were maintained at <10.0 mmo/l (1). The Leuven Study of intensive care patients demonstrated that glycemic control to a glucose target of 4.0–6.1 mmol/l reduced mortality by 40% and dramatically decreased other complications (though not cardiac outcomes) (15). Multivariate analysis demonstrated that this was due to glucose control rather than insulin therapy per se (16). However, it is unclear if these findings can be generalized to the situation of AMI. Moreover, achieving the target levels of the Leuven Study would require a major culture change. There was generally a reluctance of coronary care nursing staff to aggressively lower BGL in the HI-5 study because of the fear of hypoglycemia, which contributed to the failure to reach prescribed glucose targets in many patients.

The original premise for GIK therapy for AMI was not glucose control but the reduction of free fatty acids by insulin (17). Recently it has been recognized that insulin also has anti-inflammatory properties and suppresses reactive oxygen species under euglycemic conditions (18). Chaudhuri (19) demonstrated that insulin infusion therapy given in the postinfarct period lowers C-reactive protein, serum amyloid-A, and plasminogen activator inhibitor 1 independent of BGL. However, although ITG subjects in the HI-5 study had an attenuation of the rise in C-reactive protein compared with control subjects (20), this has not translated into improved survival. Moreover, the recent CREATE-ECLA study in which 20,201 subjects with AMI were randomized to receive GIK or usual care, also failed to demonstrate a survival benefit (5). Significantly, GIK therapy in the CREATE-ECLA study increased BGL (10.4 mmol/l after 6 h compared with 8.2 mmol/l in the control group), and the harmful effects of this may have overwhelmed any direct benefits of insulin. This result suggests that therapy with an

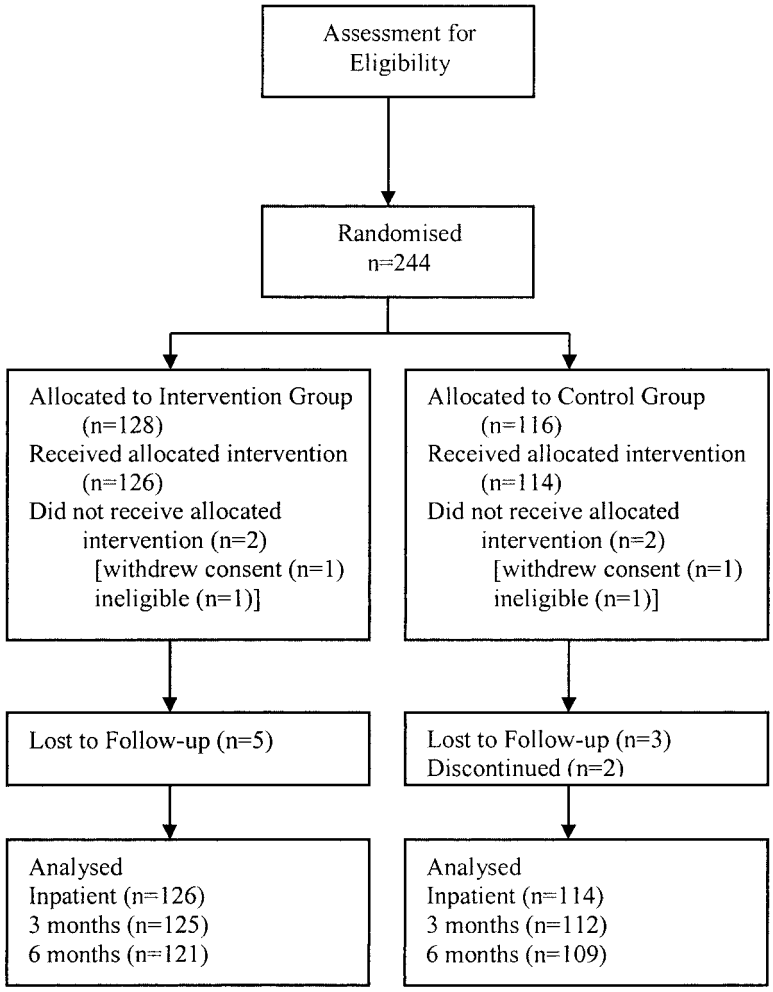

Figure 1—*Participant flow in the HI-5 study.*

insulin focus only, where the aim is to deliver large doses of insulin without regard to BGL, does not improve cardiac outcomes when other modern therapies for AMI are utilized.

Although there was no effect of insulin therapy on mortality in the HI-5 study, there was a lower incidence of cardiac failure and reinfarction. A reduction in mortality due to heart failure in patients in Killip class 1 who received primary angioplasty and GIK therapy was observed in the ECLA study (2). However, this was not reproduced in the CREATE-ECLA study (5). A recent study has found that GIK therapy reduces soluble FAS ligand and soluble FAS (21). As these are signaling molecules involved in the process of apoptosis, it has been proposed that GIK may ultimately decrease infarct size through a reduction in apoptosis in the border regions of the infarct. This might also be one explanation for the lower mortality in patients with better glucose control even though CPK levels were not lower, as reduced apoptosis would not be reflected by initial CPK levels.

The results of the HI-5 study and other recently reported trials suggest that administration of insulin per se does not reduce mortality in patients with AMI. However, it remains possible that the lower incidence of cardiac failure and reinfarction in the HI-5 study might have had some impact on mortality had a substantially larger study been achieved. Additionally, no study as yet has adequately answered the question of whether strict glycemic control, by using insulin or other means, is beneficial in AMI. The observation that BGL ≤8 mmol/l is associated with reduced mortality suggests that this is worth resolving through further clinical trials that employ aggressive insulin infusion regimens. Methodological challenges exist, as evident from the inability of our protocol and that of the DIGAMI-2 study to meet glucose targets. However, with appropriate protocol development and education, a definitive trial should be achievable.

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APPENDIX — The investigators and numbers of subjects recruited from each were: Westmead Hospital (n = 155): N.W.C., M.M., V.W., S. Boyages, D. Chipps, R. Crampton, J. Hazel, J. Holmes-Walker, J. Marks, D. Ross, H. Smith; Nepean Hospital (37): N.W.C., R. Bishop, R. Coles, D. Fitzpatrick, K. Park; Blacktown (37) and Mt. Druitt Hospitals (6): M.M., M. Cooper, M. Datyner; John Hunter Hospital (3): J. Lowe; and Auburn Hospital (2): J. Marks. The study coordinators were E. White, M. Howells and M. Wosik.

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