ACUTE CORONARY SYNDROMES

Early impact of insulin treatment on mortality for hyperglycaemic patients without known diabetes who present with an acute coronary syndrome

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Objective: To determine the effect of insulin for the management of hyperglycaemia in non-diabetic patients presenting with acute coronary syndrome.

Methods: An observational study from the MINAP (National Audit of Myocardial Infarction Project) database during 2003–5 in 201 hospitals in England and Wales. Patients were those with a final diagnosis of troponin-positive acute coronary syndrome who were not previously known to have diabetes mellitus and whose blood glucose on admission was ≥ 11 mmol/l. The main outcome measure was death at 7 and 30 days.

Results: Of 38 864 patients who were not previously known to be diabetic, 3835 (9.9%) had an admission glucose ≥ 11 mmol/l. Of patients having a clear treatment strategy, 36% received diabetic treatment (31% with insulin). Mortality at 7 and 30 days was 11.6% and 15.8%, respectively, for those receiving insulin, and 16.5% and 22.1%, respectively, for those who did not. Compared with those who received insulin, after adjustment for age, gender, co-morbidities and admission blood glucose concentration, patients who were not treated with insulin had a relative increased risk of death of 56% at 7 days and 51% at 30 days (HR 1.56, 95% CI 1.22 to 2.0, $p < 0.001$ at 7 days; HR 1.51, 95% CI 1.22 to 1.86, $p < 0.001$ at 30 days).

Conclusion: In non-diabetic patients with acute coronary syndrome and hyperglycaemia, treatment with insulin was associated with a reduction in the relative risk of death, evident within 7 days of admission, which persists at 30 days.

It is recognised that hyperglycaemia is a strong independent risk factor for patients presenting with acute coronary syndromes, and is a common finding in patients presenting with acute myocardial infarction.^{1–3} Effective glycaemic control is recommended for patients with existing diabetes who have an acute coronary syndrome, although the additional benefit of a glucose/insulin infusion over other therapy has not been confirmed.^{4–5} However, appropriate management of non-diabetic patients with hyperglycaemia remains uncertain, and the immediate benefit of insulin therapy is unproven.

We used observational data from the National Audit of Myocardial Infarction Project (MINAP) to examine the association of treatment with insulin with outcome in patients who were not previously known to be diabetic and who presented to hospital with an acute coronary syndrome and an admission blood glucose of ≥ 11.0 mmol/l.

METHODS

Details of MINAP have previously been published.^{6–7} The project uses a data set that allows examination of prehospital and in-hospital care of acute coronary syndromes. The project is based on the technological platform developed by the Central Cardiac Audit Database group.⁸ The primary purpose of the project is to provide hospitals with contemporary online analyses of their individual performance and comparisons with national aggregate data against a limited number of audit standards. The data set includes a field for random blood glucose recorded on admission and two fields to record the type of treatment (insulin/oral/diet) used in hospital and on discharge. These fields were not part of the original data set, nor was their completion mandatory, and for this reason not all hospitals recorded these data. Two hundred and one of 229 hospitals in England and Wales recorded data on treatment of

hyperglycaemia; median number 135 cases per hospital, interquartile range 59–247. Details of dosing schedules, types of insulin, duration of infusions of insulin and effects on glycaemic control are not recorded.

We analysed records of patients having a final diagnosis of troponin-positive acute coronary syndrome (both ST elevation and non-ST elevation infarctions) between January 2003 and March 2006 for whom an admission blood sugar was available. In order to prevent distortion of outcome analyses by multiple admissions, only the first admission during the study period was analysed.

We compared mortality at 7 and 30 days in the group treated with insulin (by any regime) with those who received no diabetic treatment in hospital and those in whom no treatment strategy was recorded. In the absence of follow-up data to confirm adherence to a discharge regime, or the quality of glycaemic control, analyses of outcomes are based on an assumption that medication prescribed at discharge was continued after discharge. Vital status was obtained by linkage with the Office of National Statistics using the National Health Service (NHS) number unique to each patient.

Statistics

Percentages were used to compare categorical data, and differences in percentages were expressed with the 95% CI. Continuous data were expressed using medians with interquartile ranges. Relative risk of death is presented as a percentage of deaths for patients not receiving insulin divided by the percentage of deaths for those receiving insulin. Cox regression analysis was used to calculate the relative risk of

Abbreviations: DIGAMI, Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction; HR, hazard ratio

death with 95% CI after adjustment for co-morbidity and other confounding factors.

RESULTS

Between January 2003 and March 2006, 190 033 cases of troponin-positive acute coronary syndrome were recorded in 201 collaborating hospitals; admission blood glucose was available in 56 276 (29.6%). There were no significant differences in age (median age 71.3 vs 71.7 years), gender (65.4% vs 64.7% males) or type of acute coronary syndrome (38.9% vs 38.8% ST elevation infarction) between those with and those without a record of blood glucose on admission. Of the 56 276, 52 331 (93%) had a valid NHS number with which to establish vital status. For 38 864 patients not previously diagnosed with diabetes mellitus, this was the first admission during the study period (fig 1). Of these, 3835 (9.9%) had an admission blood glucose ≥ 11 mmol/l, and form the cohort for these analyses.

Patient characteristics and co-morbidity

Patient admission characteristics are shown in table 1 and co-morbidities at admission in table 2. Patients receiving insulin were younger, and were more likely to present with ST elevation. Admission blood sugar was higher for patients who received insulin compared with both those not given any treatment and those for whom no treatment strategy was known. Pulse and blood pressure at admission were similar. Patients treated with insulin tended to have lower rates of co-morbidity. Patients for whom no treatment strategy was recorded had co-morbidities intermediate between those treated with insulin and those receiving no treatment.

Inpatient treatment

A treatment strategy provided was recorded for 2777/3835 (72%), of whom 1007 (36%) received some form of diabetic treatment and 1770 (64%) received none (fig 1). The majority of those receiving insulin were given the DIGAMI (Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction) insulin/glucose regime—607/872 (69.6%)—or an insulin pump—225/872 (25.8%).⁴ The remaining 40 (4.6%) insulin-treated patients received single-dose insulin regimes. In view of the relatively small numbers involved, patients given insulin by any regime were analysed jointly. Details of the oral diabetic medication used in hospital by 135 patients were not recorded, and further analysis of this group of patients was not performed.

Figure 1 Patient cohort.

Reperfusion treatment

Of those patients for whom a treatment strategy was recorded, 1267/2777 (45.6%) patients had a final diagnosis of ST elevation infarction. Those treated with insulin were more likely to receive some form of reperfusion treatment; 434/509 (85.3%) against 574/758 (75.7%) who received no diabetic treatment; difference 9.5%, 95% CI 5.2 to 13.9. Thrombolytic treatment was most commonly used, and primary angioplasty was used in only 25/1267 (2%) patients.

Treatment after discharge

Of 872 patients receiving insulin as an inpatient, 117 died in hospital and 128 were transferred to another hospital for further investigation. Another 12 had incomplete data on discharge treatment. For 615 who had received insulin in hospital for whom medication at discharge was specified, 254 (41.3%) were prescribed insulin and 146 (23.7%) oral diabetic medication, while 215 (35%) received no treatment.

Use of secondary prevention medication

For 1592 patients for whom details of secondary prevention medication were available, treatment use was analysed on the basis of failure to prescribe any one of the following: beta-blockers, ACE inhibitors (or angiotensin receptor blockers), aspirin or other antiplatelet drug, or a statin. For patients given insulin in hospital, 388/596 (65.1%) were given all four drugs, while for patients not given insulin 610/996 (61.2%) were given all four drugs; difference 3.9%, 95% CI -1.0 to +12.0.

Outcome

The interval to death was available for 2629/2642 (99.5%) records for patients where an in-hospital treatment strategy was recorded. The death rate at 7 and 30 days was 11.6% and 15.8%, respectively, in those receiving insulin, compared with 16.5% and 22.1%, respectively, in those not receiving insulin (table 3). The crude mortality of the group for whom no treatment strategy was recorded was intermediate between those treated and those not treated, 128/1058, 12.1% at 7 days, and 195/1058, 18.4% at 30 days.

Cox regression analysis was used to compare the risk of death after adjustment for age (by age bands; 20–54, 55–64, 65–74, ≥ 75 years), gender, pre-existing heart failure, pre-existing renal failure (creatinine > 200 mmol), admission blood glucose, presence of ST elevation infarction, and history of previous angina or myocardial infarction. Compared with those who received insulin, patients who were not treated with insulin had an adjusted relative increased risk of death of 56% at 7 days and 51% at 30 days (hazard ratio (HR) 1.56, 95% CI 1.22 to 2.0, $p < 0.001$ at 7 days; HR 1.51, 95% CI 1.22 to 1.86, $p < 0.001$ at 30 days) (table 3).

In order to negate any bias resulting from deaths occurring prior to treatment or before any potential treatment effect of insulin had occurred, regression analyses were performed after excluding 79 deaths occurring on the day of admission (median interval 12 h). The adjusted relative risk of death was slightly reduced, but remained statistically significant (table 3).

The effect of insulin treatment on risk of death was examined separately for ST segment and non-ST segment elevation infarction. The crude mortality was greater in both groups for patients who did not receive insulin, but the mortality difference between insulin-treated patients and those without treatment was more marked for patients with ST segment elevation infarction (table 4). The adjusted relative risk of death was analysed separately for ST elevation and non-ST segment elevation infarctions, using the covariates described. This was greater for untreated patients with ST elevation infarction than for those with non-ST segment elevation infarction and was

Table 1 Patient characteristics

	Any insulin treatment in hospital n = 872		No treatment n = 1770		Treatment strategy not recorded n = 1058	
Age, years	72	60–80	76	66–83	73	62–82
Male gender %	60.2	524/871	55.6	982/1766	60	634/1056
ST elevation infarction %	58.4	509/872	42.8	758/1770	46.5	492/1058
Length of stay, days	6.5	4.2–10.6	6.2	3.7–11.4	6.8	4.0–12.0
Admission glucose, mmol/l*	14.8	12.3–18.6	12.9	11.7–14.9	13.0	12.0–16.0
Admission total cholesterol, mmol/l	5.3	4.4–6.3	5.0	4.1–6.0	5.2	4.2–6.3
Heart rate at admission, beats/min	88	70–109	90	74–112	88	70–109
Systolic blood pressure, mm Hg	140	119–164	140	117–164	140	118–163
Current smoking habit %	33.1	275/832	25.2	401/1593	31	305/954

Unless stated in the table, data represent median values with interquartile ranges. Patients having oral medication or diet were excluded.

*Lower limit 11.0 mmol/l.

statistically significant. The adjusted relative risk for those with non-ST segment elevation infarction who did not receive insulin was also greater, but this did not achieve statistical significance (table 4).

As patients with ST segment elevation infarction who received insulin were more likely to receive any reperfusion treatment, the use of reperfusion treatment was added to the covariates in an analysis limited to patients with ST elevation infarction. With this adjustment, the relative increased risk of death for untreated patients was 62% at 7 days and 58% at 30 days (HR 1.62, 95% CI 1.18 to 2.22, $p = 0.003$ at 7 days; and HR 1.58, 95% CI 1.19 to 2.1, $p = 0.002$ at 30 days).

DISCUSSION

Hyperglycaemia is very common in patients presenting with acute coronary syndromes, and admission blood glucose is recognised as an independent predictor of mortality during short-term follow-up (28 days) after myocardial infarction after adjustment for glycated haemoglobin (HbA1c), age, gender and heart failure prior to the event.⁹ In a recent survey of European patients not known to be diabetic who presented with acute coronary syndromes, 36% had impaired glucose tolerance and 22% were classified as newly diagnosed diabetics after a glucose tolerance test.¹⁰ In the present study, almost 10% of patients without a previous diagnosis of diabetes mellitus had an admission blood glucose ≥ 11.0 mmol/l. It should be stressed that an admission blood sugar of 11 mmol/l is not diagnostic of diabetes in the context of an acute coronary event, and some may have normal glucose tolerance, although the majority will be diabetic or have impaired glucose tolerance.^{11 12}

We found that after adjustment for age, gender, admission blood glucose and co-morbidity, treatment with insulin was associated with a significantly lower relative risk of death by 7

and 30 days. This persisted after excluding deaths occurring on the day of admission. We did not collect information on left ventricular ejection fraction or Killip class, but there was no significant difference between groups with respect to either admission blood pressure or heart rate, and heart failure on admission is unlikely to be a confounder.

The majority of patients given insulin received infusions as described in the first DIGAMI study—consistent with recommendations current at the time.⁴ Although the second DIGAMI study did not confirm the benefits of insulin treatment, it recognised that control of blood glucose should be an integral part of the management of known type 2 diabetics with acute coronary events.⁵ As hyperglycaemic patients who were not known to be diabetic at enrolment were a minority (12.5%) in the first DIGAMI trial, the utility of insulin treatment in this group remains unproven by randomised trials. While we did not record blood glucose during treatment, we speculate that the differences in mortality outcome demonstrated in this study reflect an improvement in glycaemic control in those who received insulin. The difference was most marked in patients with ST elevation infarction, and although those with non-ST elevation infarction had a reduction in crude mortality, and an adjusted relative risk suggesting treatment benefit, this did not achieve statistical significance.

A substantial number (28%) of hyperglycaemic patients had no treatment strategy recorded, which may reflect a lack of appreciation either of the significance of hyperglycaemia or of the possibility that the patient was an undiagnosed diabetic. These patients had characteristics, co-morbidities and outcomes intermediate between those treated with insulin and those who were known not to have been offered treatment. We considered that an inability to allocate these patients was unlikely to be a source of bias.

Table 2 Co-morbidities at admission for patients having admission glucose ≥ 11 mmol/l (n = 3700)

	Any insulin treatment in hospital n = 872		No treatment n = 1770		Treatment strategy not recorded n = 1058	
	%	n	%	n	%	n
Previous angina	24.8	213/858	32.1	561/1747	27.9	290/1038
Previous AMI	18.4	158/858	25.3	446/1761	24.5	255/1041
Treated heart failure	6.6	56/851	10.1	176/1747	9.1	93/1022
Hypertension	41.8	358/857	43.2	755/1746	45.7	471/1030
Treated hyperlipidaemia	19.5	161/825	20	341/1703	28.3	280/991
Cerebrovascular disease	7.1	60/847	10.4	182/1747	9.2	94/1025
Peripheral vascular disease	3.6	31/851	4.3	76/1749	4.3	44/1023
Chronic renal failure	3.1	26/850	2.8	49/1752	3.4	35/1026
Chronic obstructive lung disease	13.4	114/853	16.4	288/1751	17.4	152/874

Patients having oral medication or diet were excluded.
AMI, acute myocardial infarction.

Table 3 Mortality, crude and adjusted relative risk of death at 7 and 30 days for all patients, and after exclusion of deaths occurring on the day of admission

All deaths	No treatment		Any insulin regime		Relative risk*	Adjusted relative risk	95% CI	p Value
	n	%	n	%				
7 days	290/1761	16.5	101/868	11.6	1.42	1.56	1.22 to 2.0	<0.001
30 days	389/1761	22.1	137/868	15.8	1.40	1.51	1.22 to 1.86	<0.001
Deaths on day of admission excluded								
1–7 days	228/1682	13.6	80/841	9.5	1.43	1.43	1.09 to 1.89	0.011
1–30 days	327/1682	19.4	116/841	13.8	1.41	1.41	1.11 to 1.78	0.004

*Relative risk; percentage dying in the untreated group divided by percentage dying in insulin-treated group.

This study has obvious limitations in relation to care provided after discharge, as we have details neither of compliance with treatment after discharge nor the degree of glycaemic control. For patients transferred to another hospital, the details of continuing treatment were also unavailable. Of those discharged from the admitting hospital, 41% continued insulin, about 24% were transferred to oral medication or diet, and for 35% diabetic medication was withdrawn. Withdrawal of treatment may have been based on formal assessment of glycometabolic state with an oral glucose tolerance test or simply on the basis of a return of normoglycaemia. While withdrawal of medication after discharge should have little impact on the 7-day mortality presented here, as the median length of stay was 6.5 days, withdrawal of treatment after discharge or failure of compliance would tend to dilute any treatment effect for those in whom continuing treatment was appropriate. The adjusted relative risk of death at 30 days was very close to that at 7 days, indicating that there was, at least, no diminution of treatment effect between 7 and 30 days.

The small difference in use of secondary prevention medication in favour of the insulin-treated group was statistically insignificant and, although data were incomplete, as details on use of secondary prevention medication were not available for some patients transferred to other hospitals, it is unlikely that this difference had any impact on 30-day mortality.

Treatment offered to patients in the study was inconsistent. We found that the majority (64%) of hyperglycaemic patients were not given treatment to lower blood glucose. The upper quartile of untreated patients had an admission blood sugar ≥ 14.9 mmol/l, suggesting that any clinical risk associated with hyperglycaemia, or the possibility that the patient had diabetes, was not recognised. Guidelines from national cardiology societies do not contain specific advice on treatment of hyperglycaemia, and some clinicians may retain a view that hyperglycaemia is simply an epiphenomenon—a marker of larger infarcts and poorer left ventricular function—resulting from catecholamine-induced changes in glucose metabolism, rather than a reflection of insulin resistance.¹³ Although there is evidence from a randomised trial within the intensive care environment of the benefits of insulin treatment for

hyperglycaemia, clinicians have not extrapolated this evidence to the care of acute coronary disease.¹⁴

There is now clear evidence that glucose itself may be toxic at higher plasma concentrations during acute coronary events. Laboratory and clinical investigations have identified a variety of mechanisms through which the adverse effects of glucose might be mediated. These include promotion of oxidative stress with impairment of endothelial function, promotion of thrombosis, inflammation and immunosuppression, and impairment of ischaemic preconditioning and the effectiveness of collateral blood supply into ischaemic zones.^{15–18} After multivariate analysis, hyperglycaemia (>11 mmol/l) is associated with increased in-hospital mortality following primary angioplasty, whereas treated diabetes without admission hyperglycaemia is not.¹⁹ Evidence of coronary microvascular dysfunction is supported by the higher frequency of the “no-reflow phenomenon” following primary percutaneous coronary intervention in hyperglycaemic patients, an increase which is seen neither in treated diabetic patients with normoglycaemia nor in individuals with elevated HbA1c.^{20–21} The persistence of hyperglycaemia (blood glucose ≥ 8.9 mmol/l from admission to at least 24 h after symptom onset) has been shown to be associated both with reduced myocardial perfusion despite patency of the infarct-related artery and with predischARGE left ventricular impairment.²² These findings suggest that both acute and persisting elevation of blood glucose, rather than an underlying “diabetic state”, promote an acute microvascular dysfunction that contributes to poorer short-term outcome. These findings may also indicate why randomised trials of insulin treatment that included patients without major elevation of glucose or which failed to achieve a reduction in glucose level or a substantial difference in glucose level between the intervention and control groups failed to demonstrate any treatment benefit.^{5–23}

The findings in this study are consistent with a meta-analysis that compared the impact of admission glucose on outcome for hyperglycaemic non-diabetic and treated diabetic patients.²⁴ In that analysis, the adverse relationship between admission blood sugar and in-hospital death was significantly worse for non-diabetics than for treated diabetic patients, and we speculate

Table 4 Seven- and 30-day mortality, relative risk and adjusted relative risk for patients with ST segment and non-ST segment elevation infarction

		No insulin treatment		Insulin treatment		Relative risk*	Adjusted relative risk	95% CI	p Value
		n	%	n	%				
ST elevation infarction	7 days	164/755	21.7	67/509	13.2	1.64	1.62	1.18 to 2.22	0.003
	30 days	193/755	25.6	80/509	15.7	1.63	1.58	1.19 to 2.10	0.002
Non-ST elevation infarction	7 days	126/1006	12.5	34/359	9.5	1.32	1.30	0.86 to 1.96	0.211
	30 days	196/1006	19.5	57/359	15.9	1.23	1.25	0.90 to 1.74	0.188

that this difference reflects the greater degree of glycaemic control achieved in diabetic patients compared with non-diabetics in whom little or no control of hyperglycaemia was achieved.

CONCLUSION—IMPLICATIONS FOR CLINICAL CARE

These observational data show for the first time that non-diabetic patients presenting with hyperglycaemia in association with an acute coronary syndrome have a better short-term prognosis when they are treated with insulin. These findings require confirmation with a randomised controlled trial. However, they support a pragmatic clinical approach of immediate treatment with insulin for patients presenting with a blood glucose ≥ 11 mmol/l, followed by a formal assessment of glucose tolerance when practicable. We do not suggest that a level of 11 mmol/l is the optimum point for introduction of treatment, as others have shown a steadily increasing mortality in relation to increasing glucose levels throughout the range of blood sugars encountered.²⁵ This suggests that a lower threshold for treatment may ultimately be considered appropriate.

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