An evaluation of the safety and efficacy of a variable rate intravenous insulin infusion in the management of hyperglycaemia in acute coronary syndrome: experience of the TITAN-ACS

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Abstract

Aim**: To assess the safety and efficacy of a variable rate intravenous insulin infusion to lower blood glucose (BG) in patients presenting with acute coronary syndrome and hyperglycaemia.**

Methods**: We evaluated the response over 24 hours of a variable rate insulin infusion with 5% dextrose and potassium chloride (40 mEq/L), to control hyperglycaemia in 776 patients with an admission BG ≥10 mmol/L in 36 UK hospitals. Patients had either ST segment elevation or non-ST segment elevation myocardial infarction and the study included both patients with or without a diagnosis of diabetes. We measured blood glucose, initially hourly, and serum potassium at admission, at 24 hours and at the time of major arrhythmias. We measured survival to 30 days.**

Results**: Median admission BG was 14.3 mmol/L (interquartile range 11.7, 18.1). At 6 hours BG was 8.0 mmol/L (6.2, 10.8), and at 20-24 hours it was 8.3 mmol/L (6.5, 11.0). Hypokalaemia due to the infusion was not observed. Hypoglycaemia (BG <3 mmol/L) occurred in 4.1% of patients, and most frequently (8.6%) in the lowest weight quartile, adjusted odds ratio 3.91, p=0.008. Thirty-day survival was not adversely affected by the occurrence of hypoglycaemia. Patients in the highest weight quartile were more likely to have glucose in the upper quartile, >10.8 mmol/L at 6 hours; adjusted odds ratio 1.82, p=0.011.**

Conclusions**: This insulin regimen was safe and effective with low rates of hypoglycaemia and no excess mortality in the hypoglycaemic subgroup. Further adjustments are required for those in the lowest and highest quartiles of weight.**

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Key words: hyperglycaemia, acute coronary syndrome (ACS), diabetes, hypoglycaemia, 30-day mortality

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Background

Despite advances in the management of acute coronary syndrome (ACS), the mortality in those who present with hyperglycaemia remains high, with a near linear relationship between admission blood glucose and the adjusted relative risk of death, across the whole spectrum of acute coronary syndromes.[1,2] Admission hyperglycaemia appears to be more strongly associated with subsequent mortality than a prior diagnosis of diabetes.[1] Furthermore, normalisation of glucose after admission has been associated with better survival in hyperglycaemic patients with ACS whether or not they are treated with insulin,[3] although a recent report raised the possibility that intravenous insulin infusions may only be of benefit for ST segment elevation myocardial infarction.[4]

While there is a powerful pathophysiological basis for the toxicity of glucose in the context of acute coronary ischaemia based on oxidative stress,[5,6] enhanced platelet activation and thrombin formation,[7] and impaired response to antiplatelet drugs,[8] the evidence base for the value of intravenous insulin given to lower glucose in ACS is weak. DIGAMI-1 remains the only randomised controlled trial to demonstrate a survival benefit for intravenous insulin compared to routine care.[9] However, the planned end point in DIGAMI-1, mortality at 3 months was neutral, and only

at 1 year was there a significant 29% reduction in mortality for the intensively treated group. It is uncertain whether this benefit can be attributed to the in-hospital intravenous insulin use or subsequent tight glycaemic control using subcutaneous insulin. Two other randomised controlled trials have not shown any survival benefit from the use of an intravenous insulin infusion.[10,11]

In addition to the limited evidence for survival benefit associated with intravenous insulin use in ACS, high rates (10–15%) of hypoglycaemia (<3 mmol/L) were reported in the randomised trials.[9-11] Although two further studies have shown that insulin-induced hypoglycaemia, as opposed to that resulting from the haemodynamic and metabolic effects of myocardial infarction, is not associated with adverse outcomes,[12,13] concern about the risks of in-hospital hypoglycaemia have increased with the publication by Garg *et al* which showed that insulin-induced hypoglycaemia as well as spontaneous hypoglycaemia is associated with increased mortality in the inpatient setting.[14] This concern about the adverse effects of hypoglycaemia in hospital inpatients continues to act as a barrier to the wider use of intravenous insulin infusion in ACS.

Against this background of concern about hypoglycaemia and a paucity of robust evidence for benefit, it is unsurprising that intravenous insulin use remains low in ACS; in patients admitted to American hospitals with ACS and having an admission glucose >11 mmol/L, only 13% received intravenous insulin.[15] Nevertheless, the majority of clinical guidelines on the management of hyperglycaemia in ACS advise the use of intravenous insulin at the time of admission and for the first 24–48 hours.[16-19]

We therefore considered that a validated and safe intravenous insulin protocol would be useful to support the wider use of insulin in accordance with current clinical guidelines.

Aim

The primary aim of the TITAN-ACS study was to assess the efficacy and safety of an intravenous insulin regimen administered with 5% dextrose and potassium chloride in treating hyperglycaemia (≥10 mmol/L) and restoring normoglycaemia in patients having ACS. This unique insulin protocol had been piloted on 50 patients admitted with ACS and hyperglycaemia to Oxford University Hospitals as part of an Association of British Clinical Diabetolgists audit.

Patients and methods

The study was performed prospectively between November 2009 and December 2011. Thirty-six hospitals in England and Wales participated. There was no restriction to recruitment on grounds of age, absence or presence of diabetes, absolute level of admission blood glucose, treatment regime, type of ACS, management strategy, or haemodynamic status. The following were excluded: those having severe non-cardiac comorbidity with an estimated prognosis of less than 6 months; those having complex metabolic disorders likely to influence glycometabolic control; pregnant females; and those for whom transfer to another hospital was imminent.

Eligible patients admitted to coronary care units with a blood glucose of ≥10 mmol/L received a variable rate intravenous insulin infusion regimen during the first 24 hours in hospital, continued for longer at the discretion of the supervising clinician. The insulin infusion consisted of 50 units Human Actrapid® in 49.5 mL sodium chloride 0.9%. This was run concurrently with 5% dextrose and potassium chloride 40 mEq/L and was infused at 30 mL/hour via a non-reflow Y connector. No adjustment to the infusion rate was made for body weight. Capillary blood glucose concentration was initially measured hourly until within the target range (4–8 mmol/L) for 2 hours, and subsequently every 2 hours. When blood glucose remained at 4–8 mmol/l for 6 hours, the infusion protocol allowed for its discontinuation, while 2-hourly checks on blood glucose were continued. If glucose increased above 8 mmol/L after stopping the infusion, it was recommended that the infusion be restarted and continued to 24 hours after which management was at the discretion of the supervising physician. Clinical management of hypoglycaemia followed local protocols. Existing diabetes medication was withdrawn for the duration of the insulin infusion with the exception of basal analogue insulin.

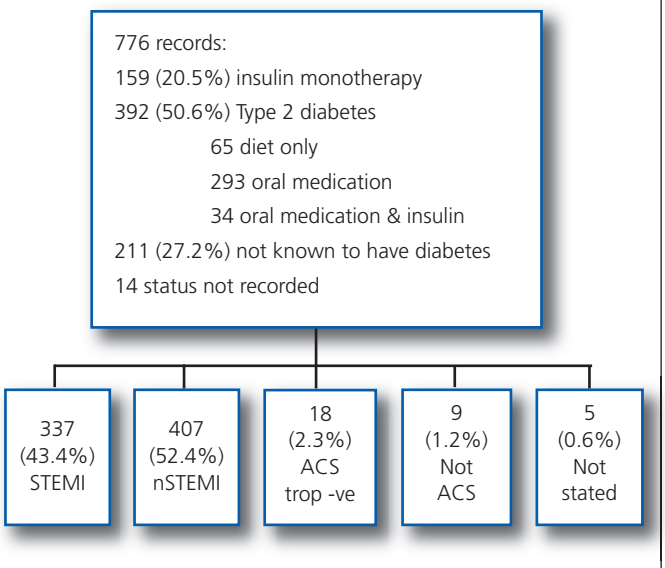
It was recommended that the infusion should be commenced as soon as possible after admission. Where the initial blood glucose was between 8 and 10 mmol/L, it was checked after 1 and 2 hours and if it exceeded 10 mmol/L the insulin infusion was started. The intravenous insulin infusion regimen used in TITAN-ACS is shown in Table 1. Serum potassium was checked on admission and at 24 hours, or if there was any sustained atrial or ventricular arrhythmia.

Data collection. The Myocardial Ischaemia National Audit project for England and Wales (MINAP) records data on admissions to coronary care units with ACS in all acute hospitals. Data collected from TITAN-ACS were entered using a dedicated module within the MINAP web-based data application.[20] The use of the MINAP application allowed immediate linkage of data concerned with the management of the ACS with the details related to management of hyperglycaemia, and to record deaths

Table 1 Variable rate intravenous insulin infusion regimen used in TITAN-ACS

Blood glucose mmol/L	Insulin infusion mL/hour
≤4	Nil. Treatment of hypoglycaemia according to local protocol
4.1–6.0	1 mL (1 unit/hour)
6.1–8.0	2 mL
8.1–10.0	3 mL
10 .1–12.0	4 mL
12.1–14.0	5 mL
≥14. 1	6 mL. If glucose remains ≥14 for over 2 hours increase insulin rate by 1 unit /hour.

Figure 1. Diabetes status and final clinical diagnosis



STEMI = ST elevation myocardial infarction; nSTEMI = non-ST elevation myocardial infarction; trop-ve = troponin negative acute coronary syndrome

via the Medical Records Information Service (MRIS).

Statistical analysis. Median values with interquartile ranges (IQR) were used to describe the range of blood glucose values. Blood glucose values are also presented as mean and standard deviations to facilitate comparisons with other work. Other summary data are also presented as means with standard deviations. The frequency distribution of categorical variables was compared using a χ^2 test. Adjusted odds ratios were calculated using multiple logistic regression analysis. Statistical analysis was performed using SPSS v18.

Results

Data were recorded on 776 patients in 36 hospitals (an average of 21.5 per hospital) presenting with suspected ACS and either with known diabetes and/or hyperglycaemia (≥10 mmol/L).

Table 2 Frequency of significant co-morbidities

	n	%
Treated hypertension	471/763	61.7
Previous myocardial infarction	247/768	32.2
Treated hyperlipidaemia	346/760	45.5
Previous angioplasty	114/765	14.9
Previous coronary artery grafting	85/767	11.1
Chronic renal failure (>200 micromol/L)	67/767	8.1
Heart failure	59/764	7.7

Of these 776, 725 had an initial admission blood glucose ≥10 mmol/L and 51 (6.1%) had a value ≥10 mmol/L on subsequent re-testing within the next 2 hours. The total cohort of 776 was used for analysis. The mean age was 68.3 years (SD13.3), and 65.7% were male. The type of ACS and diabetes treatment are shown in Figure 1. The co-morbidities of the cohort are listed in Table 2.

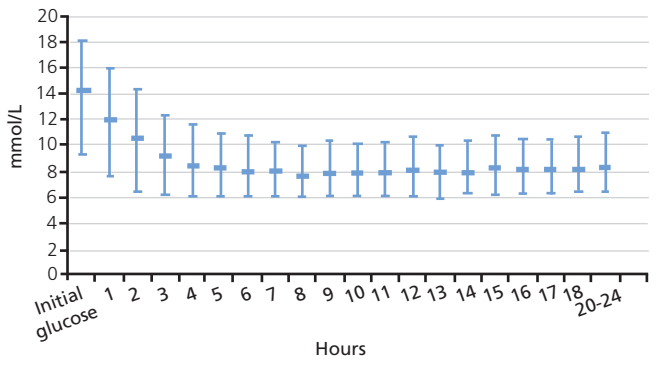
Glucometrics. The median duration of the intravenous insulin infusion was 24 hours (IQR 15.5, 35). Median blood glucose at onset of treatment was 14.3 mmol/L (11.7, 18.1), mean 15.7 mmol/L (SD 5.3). The median interval from arrival in hospital to starting the infusion was 256 minutes (IQR 156, 463). Falls in blood glucose were largely complete within 6 hours of commencing the intravenous insulin infusion, when median glucose was 8 mmol/L (IQR 6.2, 10.8), mean 8.9 mmol/L (SD 4.2). The response was similar between those with diabetes and those without known diabetes. These changes are summarised in Table 3 and graphically represented in Figure 2.

Hypoglycaemia. An episode of severe hypoglycaemia (≤3 mmol/L) was recorded during the infusion in 4.1% (32 of 776) patients and oral glucose was given for 16 episodes. In 2.4% (19 of 776) there was a single episode of hypoglycaemia, for 1.5% (12 of 776) there were 2–3 episodes, and one patient

Table 3 Capillary glucose levels in response to the intravenous insulin infusion (n = 776) including 14 records where diabetes status was not recorded

	Median (IQR) capillary glucose mmol/L			
	Not known to have diabetes n = 211	**Type 2 diabetes n = 392**	**Diabetes on insulin only n = 159**	**All patients n = 776**
Pre-infusion	13.1 (11.0, 16.8)	14.6 (11.9, 18.2)	15.7 (12.8, 20.7)	14.3 (11.7, 18.1)
1 hour	10.9 (8.6, 14.8)	12.0 (9.8, 15.6)	13.1 (10.3, 18.6)	12.0 (9.3, 16.0)
3 hours	8.4 (6.2, 10.8)	9.2 (6.6, 12.6)	10.3 (7.2, 13.8)	9.2 (6.5, 12.3)
6 hours	7.6 (6.2, 9.8)	7.9 (6.1, 10.6)	8.3 (6.3, 12.4)	8.0 (6.2, 10.8)
9 hours	7.5 (6.2, 9.6)	7.9 (6.1, 10.3)	8.5 (6.3, 11.7)	7.9 (6.2, 10.3)
12 hours	7.3 (6.2, 9.8)	8.5 (6.2, 11.3)	8.4 (6.1, 10.6)	8.1 (6.2, 10.7)
20–24 hours	7.6 (6.3, 9.8)	8.3 (6.6, 11.1)	9.2 (6.8, 12.8)	8.3 (6.5, 11.0)

Figure 2. Median (IQR) glucose values during insulin infusion using the TITAN protocol



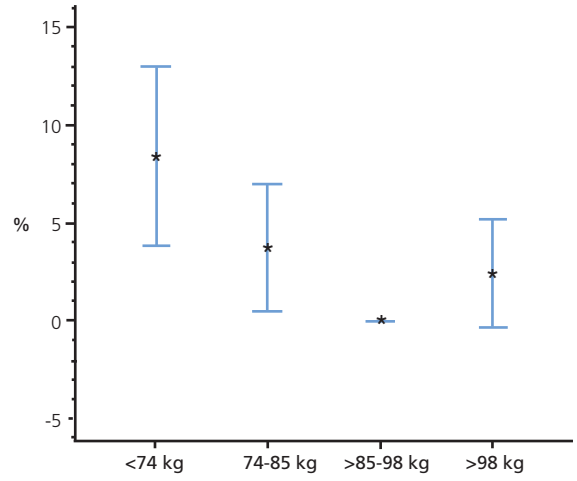
had four episodes. Hypoglycaemia was more frequent in the early part of the infusion; 53.1% (17 of 32) had a first episode of hypoglycaemia within the first 5 hours of the infusion. In 62.5% (20 of 32), hypoglycaemia developed when the previous value was already within the range of 4–8 mmol/L. Hypoglycaemia was more common in the lowest quartile of admission hyperglycaemia.

Impact of patient weight on hyperglycaemia and hypoglycaemia. Patient weight was available for 69% (539 of 776), of records. The mean rate of fall of glucose during the first 6 hours of the infusion was weight dependent. For the lightest quartile of weight the average rate of fall of glucose was 1.16 mmol/L/hour, for the intermediate quartiles the rate of fall was 1.08 and 0.97 mmol/L/hour and for the highest quartile 0.9 mmol/L/hour. After adjustment for age and serum creatinine as continuous variables and gender, type of ACS and diabetes treatments as categorical variables, the adjusted odds ratio (OR) for those in the highest quartile of weight also having a glucose value in the upper quartile (≥10.4 mmol/L) 6–8 hours after starting the infusion was 1.82, 95% CI 1.14 to 2.88, p = 0.011.

The frequency of hypoglycaemia was highest in the lowest quartile of weight; for those <74 kg it was 8.6%, 74–85 kg it was 3.0%, >85–98 kg it was 0.7% and >98 kg it was 2.0%. This is graphically represented in Figure 3. After adjustment for age and serum creatinine as continuous variables and gender, type of ACS and diabetes treatments as categorical variables, the OR for the occurrence of hypoglycaemia in the lowest quartile of weight compared to the three higher quartiles of weight was 3.91, 95% CI 1.44 to 10.6, p = 0.008. The occurrence of hypoglycaemia was also significantly associated with use of insulin monotherapy prior to admission; adjusted OR 4.4, 95% CI 1.43 to 13.5, p = 0.010.

Cardiac arrhythmias and relationship to serum potassium. The mean serum potassium on admission was 4.4 mmol/L (SD 0.64), and at 24 hours 4.3 mmol/L (SD 0.6). At the time of any arrhythmia the mean potassium was 4.3 mmol/L (SD 1). There were 59 episodes of sustained arrhythmia during the insulin infusion: 34 episodes of atrial tachycardia or fibrillation; 14 episodes of ventricular tachycardia; 11 episodes of ventricular fibrillation. Sixteen episodes of arrhythmia occurred when the

Figure 3. Rates of hypoglycaemia in relation to body weight



serum potassium that was lower than 4 mmol/L. However, where serum potassium was lower than 4 mmol/L at the time of the arrhythmia, the potassium recorded at that time reflected the admission potassium to within 0.2 mmol/L in every case. While blood glucose was not specifically measured at the time of any arrhythmia, it was noted that only two of 25 episodes of ventricular arrhythmia developed in a patient who also sustained an episode of hypoglycaemia.

Mortality outcome. Thirty-day all cause mortality was available for 96.3% (747 of 776). Overall, the 30-day mortality rate was 10.8% (81/747). In those who had one or more episodes of hypoglycaemia, 30-day mortality was 6.7% (2/30), and 11.0% (79/717) in those who did not have hypoglycaemia, χ^2 p = 0.45.

Discussion

TITAN-ACS was designed to evaluate the efficacy and safety of a simple protocol for the management of hyperglycaemia in ACS in routine hospital practice. This was tested in a cohort having a median admission blood glucose of 14.3 mmol/L (IQR 11.7, 18.1). The fall in blood glucose following the insulin infusion was essentially complete by 6 hours. An episode of severe hypoglycaemia was reported in 4.1% of patients. Hypokalaemia attributable to the infusion was not observed.

At the time the protocol for this study was devised a target range of 4–8 mmol/L was accepted practice, and became the target for TITAN-ACS. However, the NICE-SUGAR trial, based on patients on intensive care units, and therefore not directly comparable to acute coronary ischaemia, reported poorer outcomes for those having tight glucose control between 4.5 and 6 mmol/L compared with those randomised to a target of less than 10 mmol/L.[21] There is, however, no widely accepted target range. A recent consensus guideline stated 'An approximation towards normoglycaemia, with less stringent targets in those with severe co-morbidities, is a reasonable goal but exact targets are still to be defined'.[16] In the light of the present findings, and in the

absence of firm evidence, a range of 6–10 mmol/L appears realistic and achievable.

Patient weight played an important role in the response to insulin. After 6 hours there were no further falls in glucose. However, those in the upper quartile of admission glucose at 6 hours (≥10.8 mmol/L) tended to remain above 10 mmol/L throughout the first 24 hours. We found that those in the highest quartile of weight had a significantly higher adjusted OR (1.8, p=0.011) of also being in the upper quartile of glucose at 6–8 hours than those in lower quartiles of weight. Although the protocol advised an increase in insulin infusion rate where glucose remained above 14 mmol/L for 2 consecutive hours, this advice may have to be modified to a lower glucose threshold for those who are in the highest quartile of weight.

The occurrence of hypoglycaemia was also weight dependent, with the highest frequency, 8.6%, found in those in the lowest quartile of weight. The adjusted OR for development of hypoglycaemia in the lowest quartile of weight was 3.91, p=0.008. The majority of episodes of hypoglycaemia (62.5%) occurred when the previously measured blood glucose was already within the range of 4–8 mmol/L, and indicates that a lower dose of insulin may be appropriate once the blood glucose is below 8 mmol/L. This applies particularly in those with a weight in the lowest quartile (<74 kg). The occurrence of hypoglycaemia was also strongly associated with use of insulin monotherapy prior to admission and with the lowest quartile of admission hyperglycaemia.

These contrasting glycaemic outcomes demonstrate that early glycaemic responses to the variable insulin infusion should be utilised proactively to respectively increase or reduce the variable rate insulin infusion in more hyperglycaemic patients with higher body mass indices, and those of lower body mass index whose glucose falls to less than 8 mmol/L in the first 6 hours of the infusion. Hypoglycaemia is a potent source of concern amongst clinicians and there is a clear physiological rationale for harm. Hypoglycaemia induces sympatho-adrenal stimulation with potentially adverse cardiovascular consequences,[22] including QT interval prolongation,[23] and release of inflammatory cytokines that have an adverse impact on endothelial function.[24] These effects may trigger arrhythmias and exacerbate ischaemia, and this has been proposed as an explanation for the increased mortality seen with tightly controlled diabetes in the ACCORD study.[25] However, hypoglycaemia was reported in only 4.1% of patients in TITAN-ACS, and for the majority it was a single episode, this rate is lower than that in the other published randomised controlled trials (Table 4). Although the 30-day mortality was numerically lower amongst those with hypoglycaemia, the numbers were small and the difference not statistically significant, so it would be unwise to speculate a mechanism for this observation, given the already conflicting published data regarding induced hypoglycaemia and outcomes after ACS. Conceivably, the lower quartile admission glycaemic measures of those who developed hypoglycaemia may be relevant as admission hyperglycaemia does appear to exert an independently poorer prognosis.[1]

Table 4 Comparison of hypoglycaemia rates (≤3.0 mmol/L) in the major ACS and hyperglycaemia studies with those in TITAN-ACS

	Participants	Hypoglycaemia rates in %
DIGAMI-1	620	15
DIGAMI-2	1253	11.5
HI-5	240	10.3
TITAN-ACS	776	4.1

With acceptance of a higher target range and a clearer understanding of the underlying contributory factors, including low body weight, and use of insulin monotherapy, and with more cautious insulin dosing below a glucose value of 8 mmol/L, the risk of hypoglycaemia can be further reduced. In the context of close monitoring that occurs in cardiac care units, it may be that the true risk of adverse events arising as a result of insulin-induced hypoglycaemia is very small. In the present study we did not see an excess of malignant ventricular arrhythmias in those having hypoglycaemic episodes, nor did the 30-day unadjusted mortality outcome show an association between hypoglycaemic episodes and death. Two acute hospital based studies did not demonstrate adverse mortality outcomes arising from insulin-induced hypoglycaemia during ACS, as opposed to hypoglycaemia related to the underlying metabolic disturbance. However, this outcome may relate to close electrocardiographic and physiological monitoring that occurs in cardiac care units.[12,13] The recent study by Garg *et al* showed that insulin-induced hypoglycaemia as well as spontaneous hypoglycaemia is associated with increased mortality in the general hospital inpatient setting where close monitoring is not routinely practiced.[14]

There is much that is still unknown about the potential of treating hyperglycaemia with insulin. A feature common to the three randomised trials[9-11] was the extremely long mean interval, greater than 12 hours, between onset of symptoms and randomisation. The pathophysiology of acute coronary occlusion is well understood, and it is clear that any intervention aimed at reducing myocardial damage must be applied as early as possible after occlusion. In this study the time of onset of symptoms was not recorded for all patients, but a median interval from arrival to treatment of 4.25 hours indicates that opportunities for earlier control of hyperglycaemia exist. Any potential benefit from insulin may be analogous to the 'golden hour' of thrombolytic treatment.[26] Up to the present, the impact of early treatment with insulin has not been examined.

It is also not yet known whether the use of an insulin infusion is beneficial across the spectrum of ACS. DIGAMI-1, the only study to confirm a mortality benefit from treatment with insulin, was performed in the early 1990s, and although there is a lack of clarity about the type of ACS that was included in this study, it is likely that the majority of patients had ST elevation infarction. Although guidelines have advised the use of insulin treatment

Key messages

- This study provides a safe and effective validated intravenous insulin infusion regimen for use in the management of hyperglycaemia in acute coronary syndrome (ACS)
- Normoglycaemia is achieved within 6 hours
- The regimen is effective in hyperglycaemic patients with or without a diagnosis of diabetes
- Low rates of hypoglycaemia occurred compared with other studies of acute coronary syndrome and hyperglycaemia
- No excess 30-day mortality was found in patients with ACS who develop hypoglycaemia on this intravenous insulin infusion regimen
- No insulin-induced hypokalaemia was demonstrated

for all coronary syndromes, there is no definite evidence that benefit extends across the spectrum of ACS. It also remains unclear whether insulin treatment is equally applicable to patients with type 2 diabetes who are already receiving oral medication at the time of the event and to those who are not known to have diabetes.

One recent open label, randomised study suggested that intensive glucose regulation did not reduce infarct size.[27] The most recent review of extended data from the MINAP database suggested that intravenous insulin was only associated with reduced 7-day mortality amongst those with full thickness ST segment elevation myocardial infarction and that the mortality was in fact increased amongst those with non-ST segment elevation infarction.[4]

Randomised prospective trials to determine the impact of effective control of hyperglycaemia in all types of ACS thus need to be performed. The existence of a safe and effective regimen to control hyperglycaemia should provide an impetus to examine these questions.

It is recognised that this study has limitations. There was no control group and we have no comparable information on those not included in the study who would have been suitable on the basis of admission hyperglycaemia and/or known diabetes. However these numbers were minimised through regular engagement with MINAP teams in the participating hospitals.

The purpose of the TITAN-ACS study was to provide clinicians with a safe and effective infusion regimen that could be used with confidence in routine clinical care. This has been achieved for those within the middle quartiles of weight, but it is recognised that a 'one size fits all' approach is unsatisfactory and that dose adjustment must be applied to those who fall into the outer quartiles of weight in order to reduce the risk of hypoglycaemia, on the one hand, and to achieve more timely falls in glucose on the other. A protocol modified in the light of these findings is provided in Appendix 1 (see online version of article at www.bjdvd.com) which requires evaluation in a further controlled trial.

Ethical approval Following discussion with the Chairman of the Oxford Radcliffe Ethical Committee, it was agreed that this work represented service improvement and that ethical permission was not required.

Conflict of interest MS Hammersley has accepted lecture fees from Abbott Laboratories. J Birkhead, C Weston, P Winocour and G Rayman have no conflicts of interest to declare.

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Appendix 1. Suggested amended insulin regimen on basis of TITAN data

Blood glucose mmol/L	Insulin infusion ml/ hour
< 6	nil
6.1–8.0	1 mL
8.1–10.0	3 mL
10.1–12.0	4 mL
12.1–14.0	5 mL
≥14. 1	6 mL* If glucose remains ≥ 14 for over 2 hours increase insulin rate by at least 1 unit/hour.

Note: Patient response to insulin is weight dependent. Patients less than 75 kg require close monitoring of blood glucose when this falls below 10 mmol/L in order to avoid hypoglycaemia, with consideration of temporary cessation of insulin infusion once glucose levels fall below 8 mmol/L. *For patients ≥ 95 kg, consider an initial infusion rate of 7–8 mL/hour. Where blood glucose is not falling by 1 mmol/hour, consider incrementally increasing the hourly rate of insulin by at least one unit until glucose <10 mmol/L.