Project Title:
Evaluating the effectiveness of an intensified intravenous insulin infusion to achieve normoglycaemia in patients admitted with acute coronary syndrome (ACS) and hyperglycaemia: An Observational Study (TITAN-ACS)

Date and Version No: September 2009 Version 0.6 Final

Project Lead:  Dr Maggie Hammersley, Consultant Physician Nuffield Department of Medicine, Oxford. Chair Joint British Diabetes Societies Inpatient Care Group

Collaborators:  Dr P Winocour  Dept Diabetes and Endocrinology, E & N Herts NHS Trust, Chair ABCD
               Prof I B Squire  Department of Cardiovascular Sciences, University of Leicester, MINAP Academic Committee
               Dr J Birkhead  Clinical Director MINAP
               Dr C Weston  University of Swansea Medical School, Chairman MINAP Steering Group

Sponsor: Oxford Radcliffe Hospitals NHS Trust Research and Development Department

Funders  NHS Diabetes,
          Association of British Clinical Diabetologists

Steering Committee:  Dr B Prendergast: Oxford Heart Centre, British Cardiac Society
                    Dr J Thow: York Medical School
                    Dr Miles Fisher, Consultant Diabetologist, Glasgow
                    Dr S Benbow: Liverpool and Aintree NHS trust, NICE Diabetes
                    Prof S Gough: University of Birmingham Medical School
                    Prof D Matthews, Oxford Centre Diabetes, Endocrinology and Metabolism, Chair Diabetes Research Network

Management of Acute Coronary Syndrome & Hyperglycaemia Collaborative Project MINAP, ABCD and NHS Diabetes. The TITAN-ACS Study

Version 0.4 Final  September 2009
### TABLE OF CONTENTS

1. BACKGROUND ......................................................................................................... 3
2. AIM OF PROJECT ..................................................................................................... 5
3. PROJECT DESIGN .................................................................................................... 5
   3.1 Primary and Secondary Outcome Measures ...................................................... 6
      3.1.1 Primary Outcomes ......................................................................................... 6
      3.1.2 Secondary Outcomes ..................................................................................... 6
   3.2 Data collection ....................................................................................................... 7
   3.3 Data requirements ................................................................................................. 8
   3.4 Exclusions ............................................................................................................ 8
4. STATISTICS ............................................................................................................. 9
5. PROJECT TIMING ..................................................................................................... 9
6. DATA AND PATIENT CONFIDENTIALITY .............................................................. 8
7. DATA HANDLING AND RECORD KEEPING ......................................................... 9
8. REFERENCES .......................................................................................................... 11
1. BACKGROUND

Approximately 85% patients presenting with acute coronary syndromes (ACS) have dysglycaemia. There is increasing evidence that high blood glucose (BG) levels in patients with known diabetes and also those with new stress hyperglycaemia, is associated with worse outcomes in ACS and that strict glycaemic control may improve outcomes.[1-5] There have been no randomised control trials (RCTs) comparing strict glycaemic control versus less strict; hence, there are no agreed targets for glycaemic control in the management of ACS. However, there is evidence from one RCT that treatment with insulin in the acute phase and for 3 months after the event has a mortality benefit for up to 3 years [6]. Observational data from the MINAP database showed that treatment with insulin in patients without known diabetes and ACS with a glucose >= 11mmol was associated with a reduced adjusted hazard ratio of death within 7 days [7]. A recent study from the US showed improved outcomes for those in whom hyperglycaemia resolved spontaneously or with insulin treatment [8].

Where glucose potassium insulin infusions have been used (where control of blood glucose was not an aim), those with blood glucose > 10 mmol during treatment had early higher mortality than controls who had lower blood glucose, and those starting treatment earliest (<2 hours after onset) had the greatest excess mortality over controls, although this was not statistically significant. [9]

A weakness of previous studies aimed at improvement of outcome by better glycaemic control has been that the issue of delay to treatment after onset of symptoms has not been addressed, with mean delays before insulin of >12 hours [6,10]. This may be important in explaining the relative lack of benefit seen in these studies, and should be addressed.

In the MINAP database an insulin infusion is presently used for about 18% those presenting without known diabetes with an admission glucose >= 10 mmol. There is substantial inter-hospital variation, with some hospitals not using insulin for any degree of hyperglycaemia. However, the majority are using insulin for some and few are using insulin routinely. For those with known diabetes about 50% receive an insulin infusion where the presenting blood glucose is >=10 mmol and this figure appears to have declined since the publication of DIGAMI 2 in 2007 [10]

It is postulated that the negative studies and clinical uncertainty has resulted in very limited use of insulin for hyperglycaemia. On the other hand there is increasing evidence that hyperglycaemia in the context of ACS is directly harmful to myocardium, and this may explain the adverse outcome of recent RCTs examining the effect of glucose insulin potassium infusions [9]

These findings may also inhibit use of insulin by association. The lack of a generally agreed, simple and widely applicable protocol for control of hyperglycaemia may also be relevant. The present proposal has the primary purpose of addressing this need.

A pilot project was set up to establish a simple treatment regime that could safely achieve normoglycaemia in patients admitted with ACS and raised admission blood glucose in multiple care settings.[12] The pilot protocol managed patients presenting with ACS (STEMI and NSTEMI) having an admission blood glucose (BG) > 8 mmol/L using a variable-rate insulin infusion with concurrent low dose dextrose and potassium infusion. 50 patients were managed according to this pilot protocol.

Management of Acute Coronary Syndrome & Hyperglycaemia Collaborative Project MINAP, ABCD and NHS Diabetes. The TITAN-ACS Study

Version 0.4 Final September 2009
Results of the pilot study showed that 80% of patients managed according to the pilot protocol achieved a mean BG over the 1st 24 hours within the target range (4 to 8 mmol/L). Mean blood glucose for patients over the 1st 24 hours was 7.3mmol/L (standard deviation = 1.37). There was no difference between the mean blood glucose for patients on medical wards and those on coronary care and intensive care units. Rates of hypoglycaemia were low, with a 2.53% rate of mild hypoglycaemia (3 to 4 mmol/L) and a 0.63% rate of clinically significant hypoglycaemia (< 3 mmol/L).

It was concluded that this simple regime resulted in normoglycaemia for a high percentage of patients presenting with ACS and admission blood glucose >= 8 mmol without significant hypoglycaemia, and was suitable for patients managed in both high intensity clinical settings such as coronary care units and in general medical wards.

The study group determined, on the basis of evidence from the MINAP database to limit recruitment to those patients presenting with an admission glucose >= 10mmol whether known to have diagnosed diabetes or not. This represents about 15% of all patients presenting with ACS. It was considered that extending the study cohort to include all those with an admission glucose of >= 8 mmol, (approximately 30% of all ACS), would introduce significant numbers of patients having a predicted mortality close to the mean for the population as a whole.
2. AIM OF PROJECT

To evaluate effectiveness of an intravenous insulin regime with concomitant dextrose and potassium infusion for patients with ACS presenting with an admission glucose of >= 10 mmol.

To use the information derived from these data develop a guideline for management of hyperglycaemia that would be applicable for use nationally.

The following primary outcomes will be examined;

To confirm that use of a standardised insulin regime

- Was effective in achieving normoglycaemia – time to reach 8mmol
- Was effective in maintaining normoglycaemia - percentage of glucose measurements within the range 4-8 mmol.
- Was not associated with increased frequency of either mild hypoglycaemia BG < 4mmol or severe hypoglycaemia BG < 3 mmol

Secondary outcomes would be to use the MINAP audit data to examine whether there was a mortality benefit for those receiving a standardised intravenous insulin regime titrated to achieve normoglycaemia.

If the numbers recruited for the primary objective are sufficient, then the data generated in the study, together with the associated main MINAP data will be used to examine the following in an observational, hypothesis generating fashion

- comparison of treated and untreated hyperglycaemic patients from the MINAP database using matched propensity analyses with analyses performed separately for those with known diabetes and those without diagnosed diabetes
- comparison of outcome for groups of hospitals based on previous insulin use, before and after introduction of the insulin regime.
- Comparison of mortality between patients receiving the standardised insulin infusion within 0-4, 4-8 and >=8 hours after onset of symptoms.
3. PROJECT DESIGN

All acute hospitals in England and Wales will be invited to;

- use the recommended glucose--insulin-potassium regime for patients having ACS and an admission glucose $\geq 10$ mmol for the first 24 hours after admission (and longer where felt appropriate locally)
- record additional measurements* as outlined below for each patient having an admission glucose $\geq 10$ mmol (* in addition to routine MINAP data collection)

It is intended to collect records for up to 4000 treatment episodes

3.1 Primary and Secondary Outcome Measures

3.1.1 Primary Outcome

This work will be used to develop a guideline for future care of hyperglycaemia in patients presenting with ACS. The data will be examined to determine;

- safety
- efficacy
- practicality

In relation to place of treatment, type of ACS and management strategy (lysis, pPCI), clinical condition. In particular rates of mild hypoglycaemia and severe hypoglycaemia will be examined in relation to patient clinical condition, management strategy and other correlates of outcome.

3.1.2 Secondary Outcomes

The scope of secondary outcome analysis is dependent on numbers recruited.

Adjusted all cause mortality data for insulin treated patients in those centres participating in this audit using a standardised intravenous insulin infusion to achieve normoglycaemia. This group will be compared with patients in the remaining MINAP centres who are currently receiving ‘standard treatment’ which includes a large percentage of patients who do not receive any insulin treatment. Statistical analysis will be undertaken using a variety of techniques including matched historical controls from the same hospitals, and matched propensity analyses against contemporary untreated patients.

Mortality outcome will be examined against a variety of indicators of glucometric control,
Mortality outcome will be examined against the delay from onset of symptoms to treatment with insulin.
Mortality outcome will be examined against the delay from onset of symptoms to achievement of normoglycaemia (glucose < 8 mmol).
3.2 Data collection

Data will be collected from patients presenting in coronary care units (CCU) and medical admission units (MAUs) with ACS (STEMI and NSTEMI) and admission blood glucose (BG) = and > 10 mmol/l. There will be no restriction in terms of severity of the presenting ACS, or of proposed treatment modality, including pPCI. The usual MINAP dataset, including additional items for this study, will be recorded for those having insulin. Others will be included within the normal MINAP database. Analysis will be limited to first admissions during the study period.

3.3 Data requirements

The following items will be collected in addition to the routine MINAP data items;

Admission capillary and plasma glucose
Hourly capillary glucose measurements – as appropriate – up to 24 h.
Plasma potassium levels at admission, at the time of any arrhythmia, and at 24 hours.
HbA1c.
Fasting plasma glucose following discontinuation of insulin infusion (minimum of 12 hours after stopping insulin infusion)

3.4 Exclusions

- Patients having severe non cardiac co-morbidities and a prognosis of 6 months or less
- Patients having complex metabolic disorders likely to have an impact on glycometabolic control eg Cushings disease
- Pregnant females

3.5 Numbers of patients: previous MINAP experience

MINAP records 8500-9000 patients with ACS having a blood glucose >=10 mmol / year. Based on a power calculation (see below) we will aim for a target of 4000 records of insulin (regime) treated patients, about 40% of all those presenting in MINAP with glucose levels >= 10 mmol, over a period of 12 months. This requires involvement of 100 hospitals over 12 months, 40% of the total.
4. STATISTICS

In a previous observational study the 30 day mortality difference between insulin treated and untreated groups in those without known diabetes presenting with ACS was 11.6% and 16.5%.[7] Present data (2008) from MINAP shows similar mortality outcome with an overall 30 day mortality for ACS presenting with glucose >10mmol of 13%. The sample size required to demonstrate a (conservative) difference of 2% between a treated group (insulin) and a separate untreated group (no insulin), with the untreated group having a mortality of 14%, and treated 12%, is 1530 in each group assuming alpha 0.05 and beta 0.5. There are approximately equal numbers of known diabetics and ‘non diabetics’ in the MINAP database, and it is planned to analyse these separately as mortality outcomes differ in relation to presenting blood glucose. Thus 3060 treated patients would be required based on the above conservative power calculation.

5. PROJECT TIMING

- July 2009 Circulation of invitations to become involved via MINAP and ABCD
- July 2009 Responses
- July-September 2009 Development of study support material
- October 2009 – end September 2010 data collection
- November 2009 participating centres meeting

6. DATA AND PATIENT CONFIDENTIALITY

Records for treated and untreated patients will be recorded in the MINAP database and will be subject to the existing high level encryption of data. Provision of data for analysis at the end of the study will conform to the data handling protocols already established by the MINAP academic group. Analysis of data mortality tracking will be performed by linkage to the ONS mortality database, providing all cause mortality outcome.

The project team will ensure that the participants’ anonymity is maintained. All hard copy documents will be stored securely at the hospital where they were collected and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so.

7. DATA HANDLING AND RECORD KEEPING

Management of Acute Coronary Syndrome & Hyperglycaemia Collaborative Project MINAP, ABCD and NHS Diabetes. The TITAN-ACS Study
All electronic study data will be stored on the MINAP database under the care of the Central Cardiac Audit Database (CCAD). The participants will be identified by a pseudonymised NHS number. Individual hospitals will also be pseudonymised, allowing analysis at hospital level without identification.
8. REFERENCES


Management of Acute Coronary Syndrome & Hyperglycaemia Collaborative Project MINAP, ABCD and NHS Diabetes. The TITAN-ACS Study

Version 0.4 Final September 2009

**Appendix 1: Standardised Insulin Administration Protocol**

<table>
<thead>
<tr>
<th>Blood glucose</th>
<th>Insulin infusion / hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4 mmol</td>
<td>Nil. Treatment of hypoglycaemia according to local protocol</td>
</tr>
<tr>
<td>4.1 – 6.0 mmol</td>
<td>1 ml (1 u / hour)</td>
</tr>
<tr>
<td>6.1 – 8.0 mmol</td>
<td>2 ml</td>
</tr>
<tr>
<td>8.1—10.0 mmol</td>
<td>3 ml</td>
</tr>
<tr>
<td>10.1– 12.0 mmol</td>
<td>4 ml</td>
</tr>
<tr>
<td>12.1- 14.0</td>
<td>5ml</td>
</tr>
<tr>
<td>&gt;= 14.1 mmol</td>
<td>6 ml If BG remains &gt;14.1 mmol for over 2 hours call Dr to increase insulin infusion rate</td>
</tr>
</tbody>
</table>

**Appendix 2**

Study flow chart

*Sorry John was not able to cut and paste this*