

# **Surveillance report 2016 – Hyperglycaemia in acute coronary syndromes**

## **National Institute for Health and Care Excellence**

### **Surveillance programme**

#### **Surveillance proposal consultation document**

#### **Hyperglycaemia in acute coronary syndromes NICE CG130 – 4-year surveillance review**

### **Background information**

Guideline issue date: October 2011

2-year surveillance review: no update

4-year surveillance review: no update

### **Surveillance proposal for consultation**

We will not update the guideline at this time.

We will transfer the guideline to the [static list](#) because:

- A full review yielded a 'no update' decision and no major ongoing studies or research were identified as due to be published in the near future (that is, within the next 3–5 years).

### ***Reason for the proposal***

#### **New evidence**

We found 9 new studies in a search for systematic reviews and randomised controlled trials (RCTs) published between 18 December 2012 and 11 February 2016. Evidence identified in previous surveillance 2 years after

publication of the guideline was also considered. This included 3 studies identified by search. From all sources, 12 studies were considered to be relevant to the guideline.

This included new evidence on optimal inpatient metabolic management for a person presenting with acute coronary syndrome and hyperglycaemia who had or did not have a previous diagnosis of diabetes. We also identified evidence for risk factors associated with diabetes in patients with hyperglycaemia and acute coronary syndromes (ACS) who had not previously been diagnosed. Evidence identified in these areas was either supported the current recommendations or had no impact on the recommendation. We asked topic experts whether this new evidence would affect current recommendations on hyperglycaemia in acute coronary syndromes. Generally, the topic experts thought that an update was not needed.

We did not find any new evidence on information for patients with ACS and hyperglycaemia before diagnostic investigations for diabetes.

None of the new evidence considered in surveillance of this guideline was thought to have an effect on current recommendations.

Additionally, we did not identify any relevant ongoing research that is expected to publish results in the next 3–5 years.

No equalities issues were identified during the surveillance process.

### **Overall decision**

After considering all the new evidence and views of topic experts, we decided not to update this guideline, and place NICE CG130 on the static list.

### ***Further information***

See [appendix A](#): summary of new evidence from surveillance for further information.

For details of the process and update decisions that are available, see [ensuring that published guidelines are current and accurate](#) in 'Developing NICE guidelines: the manual'.

# Appendix A: summary of new evidence from surveillance

## [Adults with acute coronary syndromes and hyperglycaemia with a diagnosis of diabetes](#)

**130 – 01 What is the optimal inpatient metabolic management of hyperglycaemia in a person presenting with acute coronary syndrome and hyperglycaemia and who also has a previous diagnosis of diabetes mellitus?**

### Recommendations derived from this question

- 1.1.1 Manage hyperglycaemia in patients admitted to hospital for an acute coronary syndrome (ACS) by keeping blood glucose levels below 11.0 mmol/litre while avoiding hypoglycaemia. In the first instance, consider a dose-adjusted insulin infusion with regular monitoring of blood glucose levels.
- 1.1.2 Do not routinely offer intensive insulin therapy (an intravenous infusion of insulin and glucose with or without potassium) to manage hyperglycaemia (blood glucose above 11.0 mmol/litre) in patients admitted to hospital for an ACS unless clinically indicated.

### Surveillance decision

This review question should not be updated.

#### [Adults with acute coronary syndromes and hyperglycaemia with a diagnosis of diabetes](#)

##### **2-year surveillance summary**

A systematic review<sup>1</sup> evaluated 3 trials that randomised participants (n=2113) to an intensive blood glucose control strategy compared with a less intensive regimen in myocardial infarction. All trials included adults irrespective of their diabetic status. Intensive blood glucose control was not defined, but all 3 studies used intensive insulin therapy plus glucose with or without potassium.

Intensive blood glucose control had no significant effect on all-cause mortality. Intensive blood glucose lowering in myocardial infarction was associated with significantly higher episodes of hypoglycaemia with a 12% absolute risk increase. Intensive blood glucose lowering therapy also showed no significant improvement in rates of heart failure, arrhythmias and reinfarction. Meta-regression

analysis revealed that mortality with intensive blood glucose therapy was worse with increased length of the therapy.

##### **4-year surveillance summary**

A 20 year follow up<sup>2</sup> a multicentre RCT (DIGAMI 1) investigated the benefit of intensified insulin-based glycaemic control (Glucose insulin infusion and subcutaneous insulin) after myocardial infarction. In the original trial patients with and without previously diagnosed diabetes and with blood glucose concentrations of more than 11 mmol/L who had had a suspected acute myocardial infarction in the previous 24 h were randomly assigned to intensified insulin-based glycaemic control (n=306) for at least 3 months, or to a control group prescribed conventional glucose-lowering treatment (n=314). During a mean follow-up period of 7.3 years, 271 patients (89%) died in the intensified glycaemic control group and 285 (91%) patients died in the standard glycaemic control group. Median

survival time was statistically significantly higher in patients in the intensified glycaemic control group (7.0 years, IQR: 1.8-12.4) than in the control group (4.7 years, IQR: 1.0-11.4) (HR: 0.83, 95%CI: 0.70-0.98, P=0.027). In stratified analysis the observed benefit was only related to low cardiovascular risk patients with no previous insulin therapy.

A randomised pilot study<sup>3</sup> examined glycaemic control in type 2 diabetes patients after acute myocardial infarction (AMI). Patients (n=20) within 24 h of AMI were randomised to iGlar (insulin glargine) associated with regular insulin (iReg), or St. Care (standard intensive care unit protocol, which uses continuous insulin intravenous delivery followed by NPH (Neutral Protamine Hagedorn) insulin and iReg). Therapy was guided exclusively by capillary blood glucose (CBG), but glucometric parameters were also analysed by blinded continuous glucose monitoring system (CGMS). The mean glycaemia was higher for St. Care and compared to iGlar by by CBG or by CGMS. Percentage of time in range by CGMS was also higher for for St. Care compared with iGlar. No severe hypoglycaemia was detected by CBG, but CGMS indicated 11 (St. Care) and 7 (iGlar) excursions in four patients from each group, mostly in sulphonylurea users (six of eight patients).

A clinical trial<sup>4</sup> investigated the impact of insulin infusion protocol and conventional therapy on the blood glucose level in patients with acute coronary syndrome and diabetes mellitus. Sixty-four patients (32 in each group) with acute coronary syndrome and acute myocardial infarction with high blood sugar on admission were included. Patients in the intervention group received insulin with East Jefferson insulin infusion protocol for at least 4 hours, and in the control group, the subjects received subcutaneous insulin (conventional therapy) for at least for 48 hours. Blood glucose was significantly reduced in the two groups and the mean blood glucose level in the intervention group was significantly less compared with the control group. Hypoglycaemia was 31.2% and 25% in the intervention and control groups, respectively. Time to reach target insulin level differed significantly between the two groups (4.75 h in the intervention group and 36.93 h in the control group).

### **Topic expert feedback**

No topic expert feedback was relevant to this question.

### **Impact statement**

The evidence from the systematic review of 3 trials suggests that intensive insulin therapy does not improve mortality and may result in an increase risk of hypoglycaemia. In contrast, the 20-year follow up multicentre trial (DIGAMI 1) showed that intensified insulin therapy might increase survival time. The CG130 scope and recommendation is for inpatient metabolic management of hyperglycaemia in person presenting with ACS, however the intervention in DIGAMI-1 trial continued for 3 months. Therefore the study does not entirely meet the scope of the CG130. Moreover the extended follow up is unable to provide an answer to whether the beneficial effects is due to the acute glucose insulin infusion or long term glucose control or the combination of the two. The author also concluded that generality of the result to the present day is difficult. The original study conducted in 1995 (data collected from 1990 to 1993) and the fact that the treatment of ACS is now different to 21 years ago, (practically with regard to anti-platelet therapy and statin therapy and coronary revascularisation) may have influenced the findings. Patients with a high risk who had not been treated with insulin previously did not benefit from intensive insulin treatment at the follow up findings. The strict glycaemic control did not seem to improve survival of patients with longstanding diabetes and CV disease.

In line with the current recommendation, evidence from a small trial indicates that continuous insulin intravenous therapy is less effective at lowering hyperglycaemia than insulin glargine. Different findings between various studies might be a consequence of the available treatments, treatment goals and baseline HbA1c-levels. There is a lack of robust evidence to support the routine use of intensive insulin therapy in patients admitted to hospital for an ACS. Therefore the new evidence has no impact on the current recommendations that routinely intensive insulin therapy was not recommended unless clinically indicated.

New evidence is unlikely to change guideline recommendations.

**130 – 02 What is the optimal inpatient metabolic management for a person presenting with acute coronary syndrome and hyperglycaemia and who does not have a previous diagnosis of diabetes?**

**Recommendations derived from this question**

- 1.1.1 Manage hyperglycaemia in patients admitted to hospital for an acute coronary syndrome (ACS) by keeping blood glucose levels below 11.0 mmol/litre while avoiding hypoglycaemia. In the first instance, consider a dose-adjusted insulin infusion with regular monitoring of blood glucose levels.
- 1.1.2 Do not routinely offer intensive insulin therapy (an intravenous infusion of insulin and glucose with or without potassium) to manage hyperglycaemia (blood glucose above 11.0 mmol/litre) in patients admitted to hospital for an ACS unless clinically indicated.

**Surveillance decision**

This review question should not be updated.

*Adults with acute coronary syndromes and hyperglycaemia without a previous diagnosis of diabetes*

**2-year surveillance summary**

A clinical trial<sup>5</sup> evaluated the effect of intensive insulin control compared with conventional insulin therapy on platelet aggregation in 59 patients with ACS and hyperglycaemia.

The intensive control group received an insulin plus sodium chloride 0.9% infusion during the initial 24 hours followed by a daily subcutaneous ultra-slow insulin administration supplemented with rapid-acting insulin for meals. The conventional group received rapid-acting insulin using a sliding scale algorithm plus their usual insulin dosage. Intensive control resulted in a significant reduction in median glucose levels compared with conventional control at 24 hours and at discharge. However, hypoglycaemic episodes of less than 60 mg/dl occurred more frequently with the intensive than the conventional control. Severe hypoglycaemia was rare (n=2) and only occurred in the intensive control group.

After 24 hours, no significant difference was observed in platelet reactivity between the

intensive control group (mean standard deviation and conventional control group. Platelet reactivity was also significantly reduced at discharge in the intensive control group compared with the conventional group.

More evidence from a cohort study was also reported at the 2-year evidence update document. The study was excluded from this report as only evidence from RCTs and systematic reviews will be reported at 4-year surveillance evidence update.

**4-year surveillance summary**

A single-centre<sup>6</sup> RCT investigated the effectiveness and safety of intensive glucose management in patients with ACS who have hyperglycaemia, aiming at strict blood glucose normalisation. Patients (n=294) with ACS with an admission plasma glucose level of 140 to 288 mg/dL were eligible for inclusion. Patients either received the intravenous insulin, or the conventional expectative glucose management.

There was no statistically significant difference in median hsTropT72 (high-sensitivity troponin T value 72 hours), median AUC-CK-MB (area under the curve of creatine kinase, myocardial

band), median extent of myocardial injury in the intensive management arm, compared with the conventional arm. Before discharge, death or a spontaneous second myocardial infarction occurred in 8 patients (5.7%) in the intensive management arm vs 1 (0.7%) the conventional arm.

A clinical trial<sup>7</sup> examined the effects of peri-procedural intensive glycaemic control (IGC) during early percutaneous coronary intervention (PCI) on restenosis rate in hyperglycaemic patients with ST-segment elevation myocardial infarction (STEMI). A total of 165 hyperglycaemic patients (glucose > 140 mg/dl) with first STEMI undergoing PCI were randomised to IGC for almost 24 h after PCI followed by multidose sc insulin or conventional glycaemic control followed by conventional therapy. After insulin infusion, mean plasma glucose during the peri-procedural period was greater in the CGC group than in the IGC group. The levels of markers of oxidative stress (nitrotyrosine), inflammation (C-reactive protein, TNF-alpha), and monocyte chemoattractant-protein-1 were significantly higher in CGC patients compared with IGC patients. Moreover, IGC during PCI reduces restenosis by half (48 and 24%) at 6 months. During follow-up, there was no difference in mortality rates, glucose, inflammatory and oxidative stress markers among the groups.

Systematic review of prospective cohort studies<sup>8</sup> was carried out to examine the risk of death in patients with ST-segment elevation myocardial infarction (STEMI) especially for non-diabetic who have Impaired admission glucose (AG). The pooled risk ratio early outcomes events indicated the patients with glucose concentrations >6.1-11.1 mmol/L had a 4.38-fold higher risk of early mortality. The pooled risk ratio of late outcomes events indicated that patients with glucose concentrations >7.8-11.1 mmol/L had a 1.65-fold risk of higher late mortality based on in-hospital or 30-day survivors.

A post hoc analysis<sup>9</sup> of an RCT carried out to evaluate the association between hyperglycaemia and infarct size, myocardial salvage, and area at risk, and to assess the interaction between exenatide and hyperglycaemia. A total of 210 STEMI patients were randomised to receive intravenous exenatide or placebo before percutaneous

coronary intervention. Hyperglycaemia was associated with larger area at risk and infarct size compared with patients with normoglycaemia, but the salvage index and infarct size adjusting for area at risk did not differ between the groups. Treatment with exenatide resulted in increased salvage index both among patients with normoglycaemia and hyperglycaemia.

A randomised trial<sup>10</sup> evaluating the effects of optimised glucose control with insulin, compared with conventional control, on platelet reactivity after hospital discharge in patients with an acute coronary syndrome and hyperglycaemia .

One hundred four patients were randomised to optimised management (n=53) or conventional management (n=51). There were no differences between groups in baseline characteristics or platelet function. After 12 months of follow-up, blood glucose levels were significantly lower in the optimised treatment group. However, platelet aggregation following adenosine diphosphate stimulation showed no differences between the groups. There were no significant differences for other platelet function tests.

A post hoc analysis of an RCT<sup>11</sup> carried out to examine the influence of a tight glycaemic control on platelet reactivity in patients with hyperglycaemia, an acute coronary syndrome and poor glycaemic control. At the initial trial patients with hyperglycaemia were randomised to undergo an intensive glucose control or conventional glucose control. A total of 67 patients presented with poor glycaemic control (37 intensive, 30 conventional), while 42 had HbA1c < 6.5% (20 intensive, 22 conventional). At discharge, patients with HbA1c >6.5% had significantly reduced MPA (mycophenolic acid) with intensive glucose control compared with conventional control. Similar findings were shown with other measures of platelet function. However, glucose control strategy did not affect platelet function parameters in patients with HbA1c < 6.5%.

#### **Topic expert feedback**

No topic expert feedback was relevant to this question.

#### **Impact statement**

There is evidence from a trial that intensive glucose control in patients presenting with an

acute coronary syndrome and hyperglycaemia results in a reduction of platelet reactivity, however this is only in the presence of elevated HbA1c. Long-term optimised glucose control with insulin did not result in a reduction in platelet reactivity compared to conventional protocol. The evidence is unlikely to have an impact on NICE CG130 as none of the outcomes showed an effect on cardiovascular events.

Intensive insulin therapy showed some benefits in management of hyperglycaemia however that was accompanied by an increased risk of hypoglycaemia. In NICE CG130

hyperglycaemia was defined as 11mmol/litre and above, and a large number of the patients in the studies would not be considered hyperglycaemic under NICE guidance. New evidence suggests that intensive glucose regulation did not reduce infarct size in hyperglycaemic patients with ACS treated with PCI, and was associated with harm. Therefore the new evidence has no impact on the current recommendations.

New evidence is unlikely to change guideline recommendations.

### **130 – 03 What risk factors are associated with diabetes in patients with hyperglycaemia and ACS who have not previously been diagnosed?**

#### **Recommendations derived from this question**

- 1.1.3 Offer all patients with hyperglycaemia after ACS and without known diabetes tests for:
- HbA1c levels before discharge and
  - fasting blood glucose levels no earlier than 4 days after the onset of ACS.

These tests should not delay discharge.

- 1.1.4 Do not routinely offer oral glucose tolerance tests to patients with hyperglycaemia after ACS and without known diabetes if HbA1c and fasting blood glucose levels are within the normal range.

#### **Surveillance decision**

This review question should not be updated.

#### *Identifying people who are at high risk of developing diabetes*

##### **2-year surveillance summary**

A sub study of an RCT<sup>12</sup> was carried to provide insight into the prevalence of previously undiagnosed diabetes and to compare different methods of diagnosing diabetes in patients with ACS. Patients with ACS with elevated APG (admission plasma glucose) who participated in the BIOMArCS 2 glucose trial underwent an oral glucose tolerance test (OGTT) prior to discharge. 130 patients were included who underwent metabolic assessment. Of these, 109 had an OGTT and 13 patients had pre-existing diabetes. The test performed with a

load of 75 g glucose before discharge and preferably on day 3 of admission. The OGTT results were categorised as (previously) undiagnosed diabetes in 35% of patients and impaired glucose metabolism in 44%, so only 21% had a normal glucose metabolism. Undiagnosed diabetes could not be adequately predicted with APG, FPG (fasting plasma glucose) or HbA1c. Patients with abnormal glucose metabolism were significantly older, had higher admission HbA1c values, a higher Killip classification and more often had a prior stroke than patients with normal glucose metabolism.



#### 4-year surveillance summary

No relevant evidence was identified.

#### Topic expert feedback

OGTT appears to be the best test to assess the presence of previously undiagnosed diabetes or impaired glucose metabolism in hyperglycaemic patients with ACS.

#### Impact statement

The evidence suggests that an oral glucose tolerance test is the best way to screen for diabetes because HbA1c and fasting plasma glucose would miss a substantial proportion of patients who should be further screened for diabetes.

This is inconsistent with NICE CG130, which states that oral glucose tolerance testing should not be offered routinely if fasting plasma glucose and HbA1c are within the normal range. However, the guidance recommends

that fasting blood glucose should be taken no earlier than 4 days after the onset of ACS as blood glucose levels would be distorted as a result of an acute event. In the relevant study, the test was ideally taken on the third day and at this time the authors were unable to determine a cut-off value that had both reasonable sensitivity and specificity. Threshold levels for HbA1c and fasting blood glucose levels are not recommended in the guidance so local threshold levels used in the UK may differ from those reported in this study from the Netherlands. Because of the limitations on timing of the blood glucose tests and threshold levels the results of this small study are unlikely to have an impact on the recommendations.

New evidence is unlikely to change guideline recommendations.

### 130 – 04 What information should patients with ACS and hyperglycaemia (who are at high risk for developing diabetes) be provided before diagnostic investigations for diabetes?

#### Recommendations derived from this question

- 1.1.5 Offer patients with hyperglycaemia after ACS and without known diabetes lifestyle advice on the following:
- healthy eating in line with 'MI: secondary prevention' (NICE clinical guideline 48) and 'Obesity' (NICE clinical guideline 43)
  - physical exercise in line with 'MI: secondary prevention' (NICE clinical guideline 48) and 'Four commonly used methods to increase physical activity' (NICE public health guidance 2)
  - weight management in line with 'MI: secondary prevention' (NICE clinical guideline 48) and 'Obesity' (NICE clinical guideline 43)
  - smoking cessation in line with 'Unstable angina and NSTEMI' (NICE clinical guideline 94), 'Smoking cessation services' (NICE public health guidance 10), 'MI: secondary prevention' (NICE clinical guideline 48) and 'Brief interventions and referral for smoking cessation' (NICE public health guidance 1)
  - alcohol consumption in line with 'MI: secondary prevention' (NICE clinical guideline 48).
- 1.1.6 Advise patients without known diabetes that if they have had hyperglycaemia after an ACS they:
- are at increased risk of developing type 2 diabetes
  - should consult their GP if they experience the following symptoms:
    - frequent urination
    - excessive thirst

- weight loss
  - fatigue
  - should be offered tests for diabetes at least annually.
- 1.1.7 Inform GPs that they should offer at least annual monitoring of HbA1c and fasting blood glucose levels to people without known diabetes who have had hyperglycaemia after an ACS.

### Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

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## ***Research recommendations***

### **Priority**

#### **RR – 01 What is the optimal management of hyperglycaemia in people with acute coronary syndrome who have diagnosed or previously undiagnosed diabetes?**

No new information was identified at any surveillance review.

Excising studies on the optional management of hyperglycaemia in people with acute coronary syndromes who have diagnosed or previously undiagnosed diabetes are generally poor quality. A large randomised controlled trial is needed to be conducted for people with ACS and hyperglycaemia (blood glucose level 11 mmol/litre and over) stratified by NSTEMI (non-ST Segment elevation myocardial infarction) and STEMI and by known diabetes and without a previous diagnosis of diabetes.

Detailed information about the research recommendations is provided by CG130.

## References

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