National Institute for Health and Clinical Excellence

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# Hyperglycaemia in acute coronary syndromes

## Management of hyperglycaemia in people with acute coronary syndromes

**This guideline was incorporated in the NICE guideline on acute coronary syndromes in November 2020. The evidence and the recommendations remain unchanged.**

NICE clinical guideline 130
Developed by the Centre for Clinical Practice at NICE

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# Contents



Appendices C, D, and E are in separate files.

This guideline partially updates recommendation 1.12.3.6 in 'Type 1 diabetes' (NICE clinical guideline 15). Recommendation 1.12.3.6 is updated for the treatment of patients with threatened or actual myocardial infarction, but not stroke.

# Introduction

## *Management of hyperglycaemia in acute coronary syndromes*

This guideline covers the role of intensive insulin therapy in managing hyperglycaemia within the first 48 hours in people admitted to hospital for acute coronary syndromes (ACS). Intensive insulin therapy is defined as an intravenous infusion of insulin and glucose with or without potassium. For the purposes of this guideline, hyperglycaemia is defined as a blood glucose level above 11 mmol/litre. This definition was based on the expert opinion of the Guideline Development Group (GDG) and was agreed by consensus.

ACS encompass a spectrum of unstable coronary artery disease, ranging from unstable angina to transmural myocardial infarction. All forms of ACS begin with an inflamed and complicated fatty deposit (known as an atheromatous plaque) in a blood vessel, followed by blood clots forming on the plaque. The principles behind the presentation, investigation and management of these syndromes are similar, but there are important distinctions depending on the category of ACS.

Hyperglycaemia is common in people admitted to hospital with ACS. Recent studies found that approximately 65% of patients with acute myocardial infarction who were not known to have diabetes had impaired glucose regulation when given a glucose tolerance test.

Hyperglycaemia at the time of admission with ACS is a powerful predictor of poorer survival and increased risk of complications while in hospital, regardless of whether or not the patient has diabetes. Despite this, hyperglycaemia remains underappreciated as a risk factor in ACS and is frequently untreated.

Persistently elevated blood glucose levels during acute myocardial infarction have been shown to be associated with increased in-hospital mortality, and to be a better predictor of outcome than admission blood glucose. Management of hyperglycaemia after ACS is therefore an important clinical issue.

A wide range of national guidance is available for the care of people with diabetes in hospital with relevance to ACS patients. For example the NHS Institute for Innovation and Improvement recommends that all patients with ACS and known diabetes are referred to the inpatient diabetes team[1].

### *Drug recommendations*

The guideline does not make recommendations on drug dosage; prescribers should refer to the 'British national formulary' for this information. The guideline also assumes that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.

### *Who this guideline is for*

This document is for healthcare professionals and other staff in secondary and tertiary care who manage hyperglycaemia in people admitted for ACS. This guideline may also be relevant to healthcare professionals in primary care.

## Patient-centred care

This guideline offers best practice advice on the management of hyperglycaemia in all adults admitted to hospital for an acute coronary syndrome regardless of whether or not they have a diagnosis of diabetes.

Treatment and care should take into account patients' needs and preferences. People with ACS and hyperglycaemia should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If patients do not have the capacity to make decisions, healthcare professionals should follow the Department of Health's advice on consent (available from www.dh.gov.uk/en/DH_103643) and the

[1] http://www.institute.nhs.uk/quality_and_value/think_glucose/thinkglucose_toolkit.html

code of practice that accompanies the Mental Capacity Act (available from www.dh.gov.uk/en/SocialCare/Deliveringsocialcare/MentalCapacity). In Wales, healthcare professionals should follow advice on consent from the Welsh Government (available from www.wales.nhs.uk/consent).

Good communication between healthcare professionals and patients is essential. It should be supported by evidence-based written information tailored to the patient's needs. Treatment and care, and the information patients are given about it, should be culturally appropriate. It should also be accessible to people with additional needs such as physical, sensory or learning disabilities, and to people who do not speak or read English.

If the patient agrees, families and carers should have the opportunity to be involved in decisions about treatment and care.

# 1 Recommendations

## *1.1 List of all recommendations*

### Managing hyperglycaemia in inpatients within 48 hours of ACS

Recommendations in this section partially update recommendation 1.12.3.6 in 'Type 1 diabetes' (NICE clinical guideline 15). Recommendation 1.12.3.6 is updated for the treatment of patients with threatened or actual myocardial infarction, but not stroke.

**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.

### Identifying patients with hyperglycaemia after ACS who are at high risk of developing diabetes

**1.1.3** Offer all patients with hyperglycaemia after ACS and without known diabetes tests for:

- $HbA_{1c}$ 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 $HbA_{1c}$ and fasting blood glucose levels are within the normal range.

### Advice and ongoing monitoring for patients with hyperglycaemia after ACS and without known diabetes

**1.1.5** Offer patients with hyperglycaemia after ACS and without known diabetes lifestyle advice on the following:

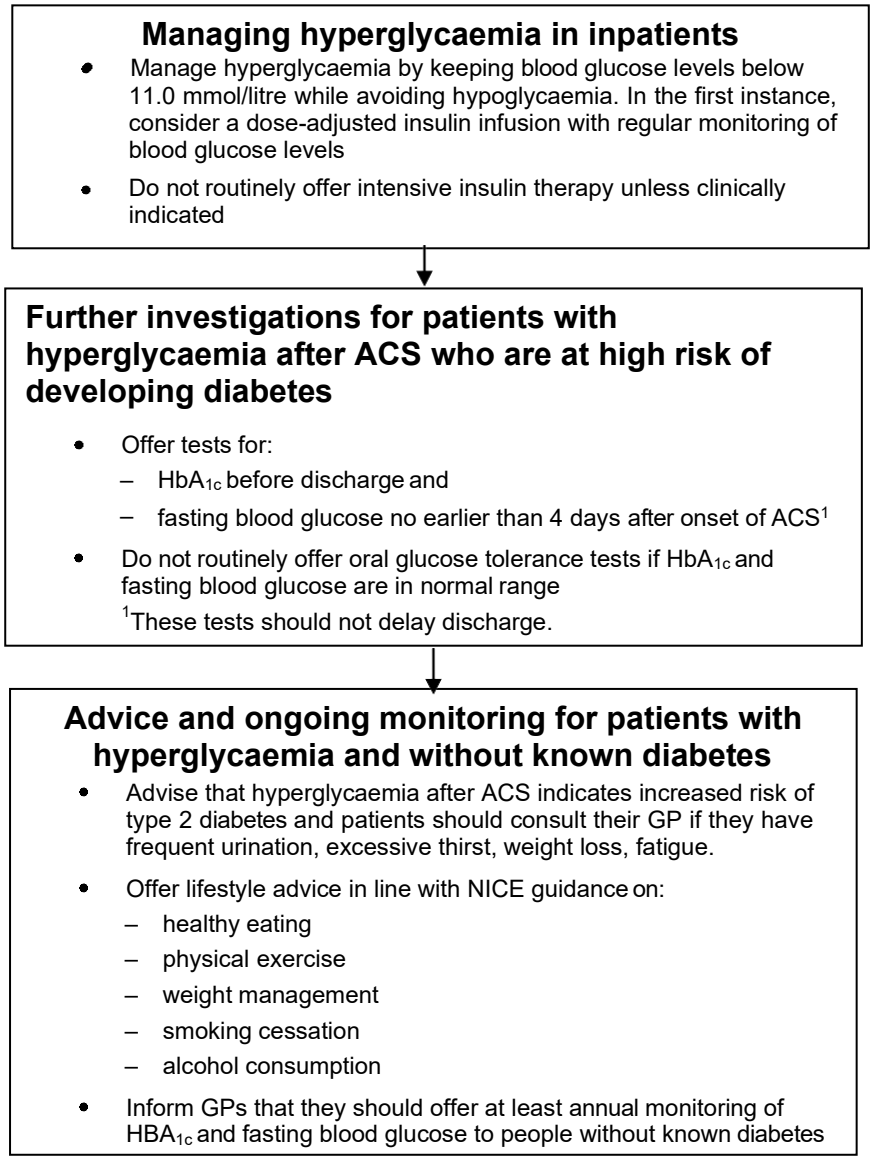
- healthy eating in line with 'MI: secondary prevention' (NICE clinical guideline 48) and 'Obesity' (NICE clinical guideline 43)
- physical exercise in line with 'MI: secondary prevention' (NICE clinical guideline 48) and 'Four commonly used methods to increase physical activity' (NICE public health 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 $HbA_{1c}$ and fasting blood glucose levels to people without known diabetes who have had hyperglycaemia after an ACS.

# 2 Care pathway



# 3 Evidence review and recommendations

For details of how this guideline was developed see appendix D.

## *3.1 Adults with acute coronary syndromes and hyperglycaemia with a diagnosis of diabetes*

### 3.1.1 Review question

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?

### 3.1.2 Evidence review

This review question focused on the use of intensive insulin therapy or standard therapy to manage hyperglycaemia in patients with ACS and diabetes. Hyperglycaemia is defined as a blood glucose level above 11 mmol/litre. This definition was based on the expert opinion of the GDG and was agreed by consensus. Nine papers were selected for this review question. The papers were based on three primary studies (Cheung et al. 2006; Malmberg et al. 1995; Malmberg et al. 2005), all of which were randomised controlled trials (RCTs) comparing an intensive insulin intervention with standard therapy. Papers were considered for inclusion if they targeted blood glucose control and provided baseline levels of blood glucose or a definition of hyperglycaemia (this may have differed from the agreed threshold of a blood glucose level above 11 mmol/litre). Papers were excluded if the trials:

- were non-randomised
- did not provide a clear definition of hyperglycaemia or report baseline levels of blood glucose in each group
- did not report diabetes status, or
- focused on patients with either hyperglycaemia or ACS but not both (for a full list of excluded papers see appendix D).

Although all papers included patients with a previous diagnosis of diabetes, some also included a proportion of patients without a previous diagnosis of diabetes. The data were extracted from subgroup analyses of patients with diabetes or were downgraded as appropriate in the GRADE table (see table 2). A series of meta-analyses were carried out for various outcomes, including mortality at different time points, rates of reinfarction and heart failure, and episodes of hypoglycaemia (see appendix E for full forest plots). Relative risks (RRs) reported are from the calculated meta-analyses. However, if adjusted values were provided in the papers, these were reported in the GRADE table.

A single GRADE table was presented for this review question. This was supported by additional summary tables of observational data extracted from two of the primary RCTs (Malmberg et al. 1995; Cheung et al. 2006). These tables present data relating to risk factors of mortality and the effect of mean blood glucose on mortality. The evidence was considered to be very low quality (see appendix E for full tables).

**Table 1 Summary of included studies for adults with ACS and hyperglycaemia with a diagnosis of diabetes**

| Author (study) | Follow-up (number of patients, n) | Definition of hyperglycaemia | Treatment | Target glycaemic range | Location | Outcomes reported for patients with diabetes |
|---|---|---|---|---|---|---|
| Malmberg et al. 1995 (DIGAMI 1) | Mean 3.4 years (n = 620) | Diabetes and blood glucose level > 11 mmol/litre or blood glucose level > 11 mmol/litre and no diabetes | Glucose–insulin infusion and subcutaneous insulin | 7–10 mmol/litre | Sweden | Mortality, reinfarction, heart failure and hypoglycaemia |
| Malmberg et al. 2005 (DIGAMI 2) | Mean 3.4 years (n = 1253[a]) | Blood glucose level > 11 mmol/litre or type 2 diabetes | Glucose–insulin infusion with insulin-based long-term glucose control | 7–10 mmol/litre | 44 centres in Sweden, Finland, Norway, Denmark, The Netherlands and UK | Mortality, reinfarction, hypoglycaemia |
| Cheung et al. 2006 (HI-5) | 3 months and 6 months (n = 240[b]) | Blood glucose level > 7.8 mmol/litre | Glucose–insulin infusion | 4–10 mmol/litre | Australia | Mortality, reinfarction and heart failure |

[a] Approximately 13% of patients did not have a previous diagnosis of diabetes.

[b] Approximately 52% of these patients did not have a previous diagnosis of diabetes.

## Table 2 GRADE table summary for patients with ACS and hyperglycaemia who also have diabetes

| Quality assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No. of patients | | Effect | | |
| No. of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | Intensive insulin therapy | Control | Relative risk (95% CI) | Absolute (mean difference) | Quality |
| **Mortality (follow-up of up to 3.4 years)** | | | | | | | | | | | |
| 3 (Malmberg et al. 1995, Malmberg et al. 2005, Cheung et al. 2006) | Randomised controlled trial | No serious limitations[f] | Serious[a] | Serious[g,h] | Serious[b] | None | 223/906 (24.6%) | 200/734 (27.2%) | RR 1.03 (0.65 to 1.62) | | VERY LOW |
| **Inpatient mortality (follow-up median 10 days)** | | | | | | | | | | | |
| 2 (Malmberg et al. 1995, Cheung et al. 2006) | Randomised controlled trial | No serious limitations[f] | Serious[a] | Serious[g,h] | Serious[b] | None | 34/432 (7.9%) | 39/428 (9.1%) | 0.87 (0.56 to 1.36) | | VERY LOW |
| **3-month mortality (follow-up of up to 3 months)** | | | | | | | | | | | |
| 2 (Malmberg et al. 1995, Cheung et al. 2006) | Randomised controlled trial | No serious limitations[f] | Serious[a] | Serious[g] | Serious[b] | None | 47/432 (10.9%) | 51/428 (11.9%) | 0.95 (0.52 to 1.76) | | VERY LOW |
| **Reinfarction (follow-up median 2 years)** | | | | | | | | | | | |
| 3 (Malmberg et al. 1995, Malmberg et al. 2005, Cheung et al. 2006) | Randomised controlled trial | No serious limitations[f] | Serious[a] | Serious[g,h] | Serious[b] | None | 79/844 (9.4%) | 69/672 (10.2%) | 1.19 (0.7 to 2.04) | | VERY LOW |
| **Heart failure (follow-up of up to 10 days)** | | | | | | | | | | | |
| 2 (Malmberg et al. 1995, Cheung et al. 2006) | Randomised controlled trial | No serious limitations[f] | Serious[a] | Serious[g,h] | Serious[b] | None | 169/432 (39.1%) | 177/428 (41.3%) | 0.81 (0.44 to 1.49) | | VERY LOW |

| Quality assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No. of patients | | Effect | | |
| No. of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | Intensive insulin therapy | Control | Relative risk (95% CI) | Absolute (mean difference) | Quality |
| **Hypoglycaemia (follow-up mean 24 hours)** | | | | | | | | | | | |
| 2 (Malmberg et al. 1995, Malmberg et al. 2005) | Randomised controlled trial | No serious limitations[f] | Serious[a] | Serious[g] | Serious[b] | None | 106/780 (13.6%) | 4/621 (0.006%) | 19.32 (5.79 to 64.41) | | VERY LOW |
| **Measure of blood glucose (follow-up mean 24 hours)** | | | | | | | | | | | |
| 2 (Malmberg et al. 1995, Malmberg et al. 2005) | Randomised controlled trial | No serious limitations[f] | Serious[a] | Serious[g] | Serious[b] | None | 780 | 620 | - | −1.49 mmol/litre (−2.66 to −0.31) | VERY LOW |
| **Subgroup analyses of mortality by mean blood glucose level < 8 mmol/litre and > 8 mmol/litre in the first 24 hours[d]** | | | | | | | | | | | |
| 1 (Cheung et al. 2006) | Randomised controlled trial | No serious limitations[f] | Serious[a] | No serious indirectness | Serious[b] | None | Inpatient mortality (adj OR 7.2, 95% CI 0.9 to 58.9, p = 0.07)<br>3-month mortality (adj OR 4.7, 95% CI 1.0 to 22.4, p = 0.05)<br>6-month mortality (adj OR 5.6, 95% CI 1.2 to 26.1, p = 0.03) | | | | VERY LOW |
| **Subgroup analyses of 1-year mortality stratified by risk[e]** | | | | | | | | | | | |
| 1 (Malmberg et al. 1995) | Randomised controlled trial | No serious limitations[f] | Serious[a] | Serious[g] | Serious[b] | None | No previous insulin and low risk (RR 0.48, 95% CI 0.25 to 0.92, p = 0.03)<br>No previous insulin and high risk (RR 0.85, 95% CI 0.50 to 1.45, p = 0.55)<br>Previous insulin and low risk (RR 0.86, 95% CI 0.42 to 1.78, p = 0.68)<br>Previous insulin and high risk (RR 0.78, 95% CI 0.49 to 1.26, p = 0.31) | | | | VERY LOW |

| Quality assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No. of patients | | Effect | | Quality |
| No. of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | Intensive insulin therapy | Control | Relative risk (95% CI) | Absolute (mean difference) | |
| **Subgroup analyses of mortality up to 3.4 years stratified by risk[e]** | | | | | | | | | | | |
| 1 (Malmberg et al. 1995) | Randomised controlled trial | No serious limitations[f] | Serious[a] | Serious[g] | Serious[b] | None | No previous insulin and low risk (RR 0.54, 95% CI 0.35 to 0.84, p = 0.005)<br>No previous insulin and high risk (RR 1.02, 95% CI 0.74 to 1.40, p = 0.91)<br>Previous insulin and low risk (RR 0.74, 95% CI 0.45 to 1.23 p = 0.25)<br>Previous insulin and high risk (RR 0.82, 95% CI 0.59 to 1.13 p = 0.22) | | | | VERY LOW |

[a] Studies carried out in various countries where current practice for standard care was thought to have varied.

[b] Wide confidence intervals.

[c] Cheung et al. 2006 reported episodes of hypoglycaemia for all patients (with and without diabetes) and are not reported here.

[d] Observational data on mortality extracted from the HI-5 study; this starts at low quality in GRADE.

[e] High-risk patients were those that fulfilled two or more of the following criteria: age older than 70 years, history of previous myocardial infarction, history of congestive heart failure, current treatment with digitalis.

[f] The Guideline Development Group considered downgrading based on the lack of blinding in this study; however, it was felt that it may not be feasible to conduct a blinded study in this situation.

[g] The DIGAMI 1 study (Malmberg et al. 1995) included a small number of patients who did not have a previous diagnosis of diabetes (approximately 13%).

[h] The HI-5 study (Cheung et al. 2006) included a large number of patients who did not have a previous diagnosis of diabetes for this outcome (approximately 52%).

Abbreviations: adj, adjusted for age, gender and cardiac intervention (percutaneous transluminal coronary angiography or thrombolysis); 95% CI, 95% confidence interval; OR, odds ratio; RR, relative risk.

See appendix E for the evidence tables in full.

### 3.1.3 Evidence statements

For details of how the evidence is graded, see 'The guidelines manual'.

*3.1.3.1* *Very low-quality evidence from three studies, with a total of 1640 patients, showed that intensive insulin did not significantly reduce overall mortality compared with standard care after a follow-up of up to 3.4 years (RR 1.03 , 95% confidence interval [CI] 0.65 to 1.62).*

*3.1.3.2* *Very low-quality evidence from two studies, with a total of 860 patients, showed that intensive insulin did not significantly reduce inpatient mortality compared with standard care (RR 0.87, 95% CI 0.56 to 1.36).*

*3.1.3.3* *Very low-quality evidence from two studies, with a total of 860 patients, showed that intensive insulin did not significantly reduce mortality compared with standard care at a 3-month follow-up (RR 0.95, 95% CI 0.52 to 1.76).*

*3.1.3.4* *Very low-quality evidence from two studies, with a total of 1516 patients, showed that intensive insulin did not significantly reduce subsequent reinfarction compared with standard care after a median follow-up of 2 years (RR 1.19, 95% CI 0.7 to 2.04).*

*3.1.3.5* *Very low-quality evidence from two studies, with a total of 860 patients, showed that intensive insulin did not significantly reduce subsequent inpatient heart failure compared with standard care (RR 0.81, 95% CI 0.44 to 1.49).*

*3.1.3.6* *Very low-quality evidence from two studies, with a total of 1401 patients, showed that hypoglycaemic events were significantly more likely in the intensive insulin group than in the standard care group during the initial 24 hours of treatment (RR 19.32, 95% CI 5.79 to 64.41).*

*3.1.3.7 Very low-quality evidence from two studies, with a total of 1400 patients, showed that intensive insulin significantly reduced mean blood glucose levels compared with standard care after 24 hours (mean difference −1.49, 95% CI −2.66 to −0.31).*

*3.1.3.8 Very low-quality evidence from one study with 240 patients showed that achieving a blood glucose level of 8 mmol/litre or less 24 hours after administration of intensive insulin was associated with lower mortality during inpatient stay (adjusted odds ratio [OR] 7.2, 95% CI 0.9 to 58.9) and at a 6-month follow-up (adjusted OR 5.6, 95% CI 1.2 to 26.1).*

*3.1.3.9 Very low-quality evidence from one study with 272 patients showed that intensive insulin was associated with a reduced 1-year mortality in low-risk patients who hadn't had previous insulin therapy compared with those who received standard care (RR 0.48, 95% CI 0.25 to 0.92).*

*3.1.3.10 Very low-quality evidence from one study with 272 patients showed that intensive insulin was associated with a reduced mortality at follow-up of a median of 3.4 years in low-risk patients who hadn't had previous insulin therapy compared with those who received standard care (RR 0.54, 95% CI 0.35 to 0.84).*

### 3.1.4 Health economic assessment

After careful consideration and discussion, the GDG concluded that the evidence did not show intensive insulin therapy to be significantly associated with a reduction in outcomes such as inpatient mortality, long-term mortality and reinfarction. The GDG also took into account the increased risk of harm (hypoglycaemia) associated with intensive insulin therapy. The GDG recommended that intensive insulin therapy should not be routinely used to manage hyperglycaemia in people with pre-existing diabetes who present with a primary diagnosis of ACS.

It would be inappropriate to conduct an economic analysis because there is a lack of evidence to support the use of intensive insulin therapy, and it is clearly more expensive than standard care. The incremental cost of using intensive insulin therapy to manage hyperglycaemia in patients with ACS and pre-existing diabetes was estimated to be £103. Table 3 provides an estimate of resource use and unit costs for managing hyperglycaemia using intensive insulin therapy compared with standard care.

Intensive insulin therapy is defined as an intravenous infusion of insulin and glucose with or without potassium. Based on GDG consensus, standard care (current practice) for people with pre-existing diabetes would include pre-filled insulin, diabetes specialist nurse time and an intravenous cannula. Those on intensive insulin therapy will require 12–24 glucose strip tests daily compared with 8–12 a day for standard care. Thus up to 24 additional test strips would be needed over 48 hours for intensive insulin therapy. See table 3 for further details.

**Table 3 Estimated resource use for intensive insulin therapy per hospital stay for 48 hours in patients with pre-existing diabetes**

| Description | Unit cost [£] | Ranges [£] | Intensive (48 hours) [£] | Standard (48 hours) [£] | Reference |
|---|---|---|---|---|---|
| 1 litre fluid with 20 or 40 mmol potassium chloride (3 litres/24 hours, 6 litres/48 hours) | 1.27 | | 7.62 | 0.00 | BNF |
| Sodium chloride 50 ml (3/24 hours, 6/48 hours) | 1.00 | | 6.00 | 0.00 | BNF |
| 50 ml Luer-Lok syringe (3/24 hours, 6/48 hours) | 0.33 | | 1.32 | 0.00 | Costing |
| Insulin syringe (3/24 hours, 6/48 hours) | 0.11 | | 0.66 | 0.00 | BNF |
| Intravenous extension (3/24 hours, 6/48 hours) | 0.55 | (0.10 to 0.95) | 3.30 | 0.00 | GDG |
| Glucose meter test strip or biochemistry (12 additional tests/24 hours, 24/48 hours) | 14.25 (50-strip pack) | (14.25 to 14.89) | 7.125 | 0.00 | BNF |
| Intravenous cannula (BD Venflon Pro) | 0.76 (1+) 0.70 (50+) 0.66 (500+) | | 0.66 | 0.66 | Costing |

| | | | | | |
|---|---|---|---|---|---|
| Dressing IV vapour-permeable adhesive film sterile 6 x 7 cm ported cannula (Tegaderm IV 3M) | 30.15 (pack of 100) | | 0.30 | 0.30 | Costing |
| Pre-filled insulin 1 or 2 per patient (50 u/50 ml) | 9.50 | 9 to 11 | 19 | 19 | Costing |
| Diabetes specialist nurse 30–45 minutes band 6 or 7 (depending on region/trust) | 54 (per hour of client contact) | (31 to 77) | 40.50 | 40.50 | PSSRU (2010) |
| Additional staff time per hospital stay, 140 minutes: blood glucose test (5 minutes/test x 12 additional tests per 24 hours = 60 minutes/24 hours; 120 minutes/hospital stay), infusion bag preparation (10 minutes per bag x 2 = 20 minutes) | 33 (gross pay Band 6 nurse) | (22 to 60) | 77 | 0.00 | PSSRU (2010) |
| Estimated cost per hospital stay (48 hours) | | | 163.485 | 60.46 | |
| Incremental cost | | | | £103.025 | |

### 3.1.5 Evidence to recommendations

The GDG discussed the criteria used in the GRADE profiles for evaluating the evidence and agreed that the evidence was of low quality. The GDG discussed the importance of the acute management of hyperglycaemia in this population in relation to the outcomes defined in the review protocol. The GDG agreed that, in this patient population, factors such as following up patients beyond the acute phase (the first 48 hours after admission) would have a bigger influence on outcomes than intensive insulin therapy.

Overall, the evidence showed that intensive insulin therapy had no statistically significant effect on overall mortality, although the DIGAMI 1 study showed a statistically significant reduction in mortality. The GDG discussed the results of DIGAMI 1 (Malmberg et al. 1995) but felt that treatment of ACS is now different compared with when the study was conducted in 1995, particularly with regard to anti-platelet therapy, statin therapy and coronary revascularisation, and may have had an impact on the findings. The GDG felt that further subgroup analyses of the DIGAMI 1 data, which showed that

intensive insulin therapy was associated with decreased mortality in low-risk patients with no previous insulin therapy, were underpowered (that is, the trial was designed to recruit enough participants to demonstrate the expected treatment effect in the whole population, not in individual subgroups). The group also noted that the initial findings of DIGAMI 1 were not replicated in the DIGAMI 2 study conducted in 2005 or in the HI-5 study (Cheung et al. 2006). However, the GDG recognised that the DIGAMI 2 study was underpowered, did not reach the pre-specified glucose endpoints and there was not an adequate separation of the three groups in terms of blood glucose levels. The GDG also agreed that further observational analyses from the HI-5 study, which showed that achieving target blood glucose levels of 8 mmol/litre or less was associated with lower inpatient mortality and 3-month mortality, were also underpowered.

Although the evidence did not show intensive insulin therapy to be significantly associated with a reduction in outcomes such as mortality, the GDG felt that there would still be a group of people who would present with hyperglycaemia with underlying glucometabolic morbidities, such as diabetic ketoacidosis and hyperglycaemic hyperosmolar syndrome. It was felt that in this group of patients hyperglycaemia should be managed aggressively, but the GDG agreed that the evidence for this population had not been reviewed. The GDG recognised that the risk of adverse events associated with hyperglycaemia that is not managed appropriately is high and felt that a separate recommendation should be made to ensure that hyperglycaemia is managed using methods other than intensive insulin therapy. The GDG discussed an example of a local protocol that included a target blood glucose level of less than 11 mmol/litre. This level was agreed because it was the upper limit of the target blood glucose level used in the included studies. The GDG did not set a minimum glucose level because this varied across the studies and the GDG wanted to avoid an arbitrary figure.

### 3.1.6 Recommendations and research recommendations for people with ACS and hyperglycaemia with a diagnosis of diabetes

**Recommendations**

**Recommendation 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.

**Recommendation 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.

**Research recommendations**

See appendix B for full details of the research recommendation.

**Research recommendation B1**

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

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

### 3.2.1 Review question

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?

### 3.2.2 Evidence review

This review question focused on the use of intensive insulin therapy or standard therapy to manage hyperglycaemia in patients with ACS without a previous diagnosis of diabetes. Hyperglycaemia is defined as a blood glucose level above 11 mmol/litre. This definition was based on the expert opinion of the GDG and was agreed by consensus. Three studies were selected for this review question, two papers (Cheung et al. 2006; van der Horst et al. 2003) were RCTs comparing an intensive insulin intervention with standard therapy. The remaining paper (Weston et al. 2007) was an observational study using audit data from the Myocardial Ischaemia National Audit Project (MINAP). This observational paper was included because it was a large UK-based study looking specifically at patients with ACS and hyperglycaemia who had no previous diagnosis of diabetes.

Papers were considered for inclusion if they targeted blood glucose control and provided baseline levels of blood glucose or a definition of hyperglycaemia (this may have differed from the agreed threshold of a blood glucose level above 11 mmol/litre). Papers were excluded if they:

- focused on patients with diabetes, unless they provided subgroup analyses by diabetes status
- did not provide a clear definition of hyperglycaemia or report baseline levels of blood glucose in each group, or
- focused on patients with either ACS or hyperglycaemia but not both (for a full list of excluded papers see appendix D).

Although all papers included patients without a previous diagnosis of diabetes, some also included a proportion of patients with a previous diagnosis of diabetes. The data were extracted from subgroup analyses of patients without diabetes or were downgraded as appropriate in the GRADE table (see table 5).

A series of meta-analyses were carried out for various outcomes, including mortality at different time points, rates of heart failure, reinfarction and any composite endpoint, which included death, recurrent infarction or repeat

angioplasty (see appendix E for full forest plots). Relative risks reported are from the calculated meta-analyses. However, if adjusted values were provided in the papers, these were reported in the GRADE table.

**Table 4 Summary of included studies for adults with ACS and hyperglycaemia without a diagnosis of diabetes**

| Author/study | Follow-up (number of patients, n) | Definition of hyperglycaemia | Treatment | Target glycaemic range | Location | Outcomes reported for patients without diabetes |
|---|---|---|---|---|---|---|
| Weston et al. 2007 (MINAP) | None past the inpatient stay (n = 2642) | ≥ 11 mmol/litre | Insulin was given to 31% (872/2777) of patients who had treatment strategy recorded. Intensive glucose-insulin given to approximately 70% of these patients, 26% of patients were given insulin pump and 5% a single dose | Those given intensive glucose-insulin were according to DIGAMI protocol (7–10 mmol/litre) | UK | Mortality at 7 and 30 days |
| Cheung et al. 2006 (HI-5) | 6 months (n = 240[a]) | ≥ 7.8 mmol/litre | Glucose-insulin infusion | 4–10 mmol/litre | Australia | Heart failure and reinfarction |
| Van der Horst et al. 2003 | 30 days (n = 940[b]) | Median blood glucose 8.5 mmol/litre in both groups | Glucose-insulin-potassium infusion | 7–11 mmol/litre | The Netherlands | 30-day mortality, reinfarction and adverse events |
| [a] Approximately 48% of these patients had a previous diagnosis of diabetes.<br>[b] Approximately 10% of these patients had a previous diagnosis of diabetes. | | | | | | |

## Table 5 GRADE table summary for patients with ACS and hyperglycaemia and without a previous diagnosis of diabetes

| Quality assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No. of patients | | Effect | | Quality |
| No. of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | Intensive insulin | Standard therapy | Relative risk (95% CI) | Absolute | |
| **30-day mortality** | | | | | | | | | | | |
| 1 (Weston et al. 2007) | Observational study | Serious[a] | No serious inconsistency | No serious indirectness | Serious[b] | None | 116/841 (13.8%) | 327/1682 (19.4%) | 0.71 (0.58 to 0.86) | 6 fewer per 100 (from 3 fewer to 8 fewer) | VERY LOW |
| **30-day mortality** | | | | | | | | | | | |
| 1 (Van der Horst et al. 2003) | Randomised controlled trial | No serious limitations[c] | Serious[d] | Serious[e] | Serious[b] | None | 21/426 (4.9%) | 21/415 (5.1%) | 0.97 (0.52 to 1.81) | 0 fewer per 100 (from 5 fewer to −5 more) | VERY LOW |
| **7-day mortality (follow-up mean 7 days)** | | | | | | | | | | | |
| 1 (Weston et al. 2007) | Observational study | Serious[a] | No serious inconsistency | No serious indirectness | Serious[b] | None | 80/841 (9.5%) | 228/1682 (13.6%) | 0.70 (0.55 to 0.89) | 4 fewer per 100 (from 1 fewer to 6 fewer) | VERY LOW |
| **Inpatient heart failure** | | | | | | | | | | | |
| 1(Cheung et al. 2006) | Randomised controlled trial | No serious limitations[c] | Serious[d] | No serious indirectness | Very serious[g] | None | 7/62 (11.3%) | 17/62 (27.4%) | 0.41 (0.18 to 0.92) | 16 fewer per 100 (from 2 fewer to 22 more) | VERY LOW |
| **Reinfarction (follow-up of up to 3 months)** | | | | | | | | | | | |
| 2 (Cheung et al. 2006, Van der Horst et al. 2003) | Randomised controlled trial | No serious limitations[c] | Serious[d] | Serious[h,i] | Very serious[g] | None | 7/538 (1.3%) | 10/526 (2.1%) | 0.70 (0.27 to 1.82) | 1 fewer per 100 (from 1 fewer to 2 more) | VERY LOW |

| Quality assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No. of patients | | Effect | | |
| No. of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | Intensive insulin | Standard therapy | Relative risk (95% CI) | Absolute | Quality |
| **Composite endpoint[j] (follow-up mean 30 days)** | | | | | | | | | | | |
| 1 (Van der Horst et al. 2003) | Randomised controlled trial | No serious limitations[c] | Serious[d] | Serious[i] | Serious[b] | None | 38/476 (8%) | 46/464 (9.9%) | adjusted RR 0.68[k] (0.44 to 1.05) | 3 fewer per 100 (from 6 fewer to 0 more) | VERY LOW |
| **Hypoglycaemia[l]** | | | | | | | | | | | |
| 1 (Van der Horst et al. 2003) | Randomised controlled trial | No serious limitations[c] | Serious[d] | Serious[i] | No serious imprecision | None | 0/426 | 0/415 | No adverse effects were associated with intensive insulin therapy | | LOW |
| **Subgroup analyses of mortality** | | | | | | | | | | | |
| 1 (Van der Horst et al. 2003) | Randomised controlled trial | No serious limitations[c] | Serious[d] | Serious[i] | Serious[b] | None | Killip class 1 (5/382) | Killip class 1 (14/387) | 30-day mortality (RR 0.36, 95% CI 0.13 to 0.99, p = 0.05) was statistically significantly reduced by intensive insulin therapy in patients with Killip class 1. Mortality was not statistically significantly reduced in patients treated with intensive insulin therapy with Killip class 2 (RR 0.31, 95% CI 0.03 to 3.08, p = 0.32), Killip class 3 (RR 2.14, 95% CI 0.73 to 6.28, p = 0.17) and | | VERY LOW |
| | | | | | | | Killip class 2 (1/21) | Killip class 2 (2/13) | | | |
| | | | | | | | Killip class 3 (7/12) | Killip class 3 (3/11) | | | |

| Quality assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No. of patients | | Effect | | Quality |
| No. of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | Intensive insulin | Standard therapy | Relative risk (95% CI) | Absolute | |
| | | | | | | | Killip class 4 (8/11) | Killip class 4 (2/4) | Killip class 4 (RR 1.45, 95% CI 0.51 to 4.13, p = 0.48). | | |
| 1 (Weston et al. 2007) | Observational study | Serious[a] | No serious inconsistency | No serious indirectness | Serious[b] | None | STEMI (80/509)<br>NSTEMI (57/359) | STEMI (193/755)<br>NSTEMI (196/1006) | 30-day mortality was statistically significantly reduced in STEMI patients treated with intensive insulin therapy (RR 0.61, 95% CI 0.49 to 0.78, p < 0.0001). 30 day mortality was not statistically significantly reduced in NSTEMI patients treated with intensive insulin therapy (RR 0.81, 95% CI 0.62 to 1.07, p = 0.14). This was also reported at 7 days (STEMI RR 0.61, 95% CI 0.47 to 0.79, p = 0.0002, NSTEMI RR 0.76, 95% CI 0.53 to 1.08, p = 0.13). | | VERY LOW |
| **Subgroup analyses of any composite endpoint[j]** | | | | | | | | | | | |

| Quality assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No. of patients | | Effect | | Quality |
| No. of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | Intensive insulin | Standard therapy | Relative risk (95% CI) | Absolute | |
| 1 (Van der Horst et al. 2003) | Randomised controlled trial | No serious limitations[c] | Serious[d] | Serious[i] | Serious[b] | None | 18/426 | 36/430 | Composite endpoint (adjusted RR 0.47[k], 95% CI 0.27 to 0.83, p = 0.01) was statistically significantly reduced by intensive insulin treatment in patients with Killip class 1. | | |
| **Subgroup analyses of reinfarction** | | | | | | | | | | | |
| 1 (Van der Horst et al. 2003) | Randomised controlled trial | No serious limitations[c] | Serious[d] | Serious[i] | Serious[b] | None | 3/426 | 6/430 | There was no statistically significant reduction in reinfarction in patients treated with intensive insulin therapy with Killip class 1 (adjusted RR 0.39[k], 95% CI 0.09 to 1.63, p = 0.20) | | |

[a] There was no follow-up past the inpatient stay (outcome data was extracted from Office for National Statistics data using NHS numbers to identify patients). There were differences in the collection and/or recording of data across centres because blood glucose level and treatment strategy were not always available. There was also variation in what treatment was given.

[b] 95% CI includes both negligible effect and appreciable benefit and/or harm (defined as 25% relative risk reduction or relative risk increase).

[c] The GDG considered downgrading based on the lack of blinding in this study; however, it was felt that it may not be feasible to conduct a blinded study in this situation.

[d] Study not conducted in UK and practice may vary.

[e] A median blood glucose of 8.5 mmol/litre was reported at admission, which the GDG felt may not be clinically indicative of hyperglycaemia and some patients without hyperglycaemia and a relatively low blood glucose would have been included.

[g] This has been downgraded by two levels because of a small sample size, and the confidence interval includes both negligible effect and appreciable benefit and/or harm (defined as 25% relative risk reduction or relative risk increase).

| Quality assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No. of patients | | Effect | | |
| No. of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | Intensive insulin | Standard therapy | Relative risk (95% CI) | Absolute | Quality |

[h] The HI-5 study used glucose-insulin infusion for the intervention; the Van der Horst study used glucose-insulin-potassium infusion as the intervention.

[i] The Van der Horst study included a small percentage of patients who had been diagnosed with diabetes for this outcome (approximately 10%). A median blood glucose of 8.5 mmol/litre was also reported in the Van der Horst study at admission, which the GDG felt may not be clinically indicative of hyperglycaemia and some patients without hyperglycaemia and a relatively low blood glucose would have been included.

[j] Composite endpoints include death or recurrent infarction or repeat angioplasty.

[k] Adjusted for age, gender, history, Killip class, infarct location and multivessel disease.

[l] Cheung et al. 2006 only reported hypoglycaemia for all patients (diabetes and non-diabetes) and is not reported here.

NB: Adjusted relative risks are not shown for Weston et al. (2007) because figures reported in the paper were calculated using percentage dying in the untreated group divided by percentage dying in the insulin-treated group and were not consistent with reporting with the other papers.

Abbreviations: 95% CI, 95% confidence interval; HR, hazard ratio; NSTEMI, non-ST-segment-elevation myocardial infarction; RR, relative risk; STEMI, ST-segment-elevation myocardial infarction.

See appendix E for the evidence tables in full.

### 3.2.3 Evidence statements

For details of how the evidence is graded, see 'The guidelines manual'.

*3.2.3.1* *Very low-quality evidence from one observational study of 2523 patients without previous diabetes showed a statistically significant 29% reduction in 30-day mortality in patients given intensive insulin compared with those given standard therapy (RR 0.71, 95% CI 0.58 to 0.86).*

*3.2.3.2* *Very low-quality evidence from one RCT of 841 patients without previous diabetes showed that intensive insulin did not significantly reduce 30-day mortality compared with standard care (RR 0.97, 95% CI 0.52 to 1.81).*

*3.2.3.3* *Very low-quality evidence from one observational study of 2523 patients without previous diabetes showed a statistically significant 30% reduction in 7-day mortality in patients given intensive insulin compared with those give standard therapy (RR 0.70, 95% CI 0.55 to 0.89).*

*3.2.3.4* *Very low-quality evidence from one RCT of 124 patients showed a significant 59% reduction in inpatient heart failure in patients given intensive insulin compared with those given standard therapy (RR 0.41, 95% CI 0.18 to 0.92).*

*3.2.3.5* *Very low-quality evidence from two RCTs of 1064 patients showed that intensive insulin did not significantly reduce reinfarction compared with standard care after a follow-up of up to 3 months (RR 0.70, 95% CI 0.27 to 1.82).*

*3.2.3.6* *Very low-quality evidence from one RCT of 940 patients showed that intensive insulin did not significantly reduce the occurrence of any composite endpoint (death, recurrent infarction or repeat angioplasty) compared with standard care after a follow-up of 30 days (RR 0.68, 95% CI 0.44 to 1.05).*

*3.2.3.7 Low-quality evidence from one RCT of 841 patients showed that no adverse effects were associated with intensive insulin. Very low-quality evidence from one RCT of 841 patients showed that 30-day mortality (RR 0.36, 95% CI 0.13 to 0.99, p = 0.05) was significantly reduced by intensive insulin in patients with Killip class 1. There was no statistically significant reduction in 30-day mortality in patients treated with intensive insulin with Killip class 2 (RR 0.31, 95% CI 0.03 to 3.08, p = 0.32), Killip class 3 (RR 2.14, 95% CI 0.73 to 6.28, p = 0.17) or Killip class 4 (RR 1.45, 95% CI 0.51 to 4.13, p = 0.48).*

*3.2.3.8 Very low-quality evidence from one observational study of 2523 patients showed 30-day mortality was significantly reduced in patients with ST-segment-elevation myocardial infarction (STEMI) treated with intensive insulin (RR 0.61, 95% CI 0.49 to 0.78, p < 0.0001) but not in patients with non-ST-segment-elevation myocardial infarction (NSTEMI) (RR 0.81, 95% CI 0.62 to 1.07, p = 0.14). This was also reported at 7 days (STEMI RR 0.61, 95% CI 0.47 to 0.79, p = 0.0002, NSTEMI RR 0.76, 95% CI 0.53 to 1.08, p = 0.13).*

*3.2.3.9 Very low-quality evidence from one RCT of 841 patients showed that composite endpoints were significantly reduced by intensive insulin in patients with Killip class 1 (adjusted RR 0.47, 95% CI 0.27 to 0.83, p = 0.01).*

*3.2.3.10 Very low-quality evidence from one RCT of 841 patients showed that there was no statistically significant reduction in reinfarction in patients treated with intensive insulin with Killip class 1 (adjusted RR 0.39, CI 0.09 to 1.63, p = 0.20).*

### 3.2.4 Health economic assessment

The review of clinical evidence did not show intensive insulin therapy to be more effective than standard care in managing hyperglycaemia in patients presenting with ACS without pre-existing diabetes.

It would be inappropriate to conduct an economic analysis because there is a lack of evidence to support the use of intensive insulin therapy and it is clearly more expensive than standard care. The incremental cost of using intensive insulin therapy to manage hyperglycaemia in patients with ACS without pre-existing diabetes was estimated to be £85.15 per hospital stay (table 6).

The GDG recommended that intensive insulin therapy should not be routinely used to manage hyperglycaemia in patients presenting with ACS without pre-existing diabetes. Table 6 provides an estimate of resource use and unit cost of managing hyperglycaemia using intensive insulin therapy compared with standard care.

Intensive insulin therapy is defined as an intravenous infusion of insulin and glucose with or without potassium. Based on GDG consensus, people without pre-existing diabetes would neither receive insulin nor need care from a diabetes nurse as part of standard care. Those on intensive insulin therapy would need 12–24 glucose strip tests daily compared with 2–4 a day for standard care. Thus up to 40 additional test strips would be needed over 48 hours for those on intensive insulin therapy. See table 3 for further details.

**Table 6 Estimated resource use for intensive insulin therapy per hospital stay for 48 hours in patients without pre-existing diabetes**

| Description | Unit cost [£] | Ranges [£] | Intensive (48 hours)[£] | Standard (48 hours) [£] | Reference |
|---|---|---|---|---|---|
| 1 litre fluid with 20 or 40 mmol potassium chloride (3 litres/24 hours, 6 litres/48 hours) | 1.27 | | 7.62 | 0.00 | BNF |
| Sodium chloride 50 ml (3/24 hours, 6/48 hours) | 1.00 | | 6.00 | 0.00 | BNF |
| 50 ml Luer-Lok syringe (3/24 hours, 6/48 hours) | 0.33 | | 1.32 | 0.00 | Costing |
| Insulin syringe (3/24 hours, 6/48 hours) | 0.11 | | 0.66 | 0.00 | BNF |
| Intravenous extension (3/24 hours, 6/48 hours) | 0.55 | (0.10 to 0.95) | 3.30 | 0.00 | GDG |
| Glucose meter test strip or biochemistry (20 additional tests/24 hours, 40/48 hours) | 14.25 (50-strip pack) | (14.25 to 14.89) | 14.25 | 0.00 | BNF |
| Intravenous cannula (BD Venflon Pro) | 0.76 (1+) 0.70 (50+) 0.66 (500+) | | 0.66 | 0.66 | Costing |
| Dressing IV vapour-permeable adhesive film sterile 6 x 7 cm ported cannula (Tegaderm IV 3M) | 30.15 (pack of 100) | | 0.30 | 0.30 | Costing |
| Pre-filled insulin 1 or 2 per patient( 50 u/50 ml) | 9.50 | 9 to 11 | 19 | 0.00 | Costing |
| Additional staff time per hospital stay 60 minutes: blood glucose test (5 minutes/test x 4 additional tests per 24 hours = 20 minutes/24 hours; 40 minutes/inpatient stay), infusion bag preparation (10 minutes per bag x 2 = 20 minutes) | 33 Gross pay Band 6 nurse | (22 to 60) | 33 | 0.00 | PSSRU (2010) |
| Estimated cost per hospital stay (48 hours) | | | 86.11 | 0.96 | |
| Incremental cost | | | £85.15 | | |

### 3.2.5 Evidence to recommendations

The GDG agreed that overall the evidence presented was of very low quality and felt that the studies did not directly answer the review question.

Specifically, the group felt that the reductions in mortality shown in the observational data from MINAP may have been affected by factors other than intensive insulin therapy. It acknowledged that because MINAP was not a randomised controlled trial, patients may have received different care and this may have affected the outcome. In addition, important outcomes such as hypoglycaemia were not reported and may have shown that intensive insulin therapy was associated with adverse events.

Similarly, the group agreed that the RCT conducted by Van der Horst may have included some patients who did not have hyperglycaemia. The median blood glucose level in both the treatment and control groups was 8 mmol/litre, which the group considered to be low and not clinically indicative of hyperglycaemia. It was also noted that for some outcomes the Van der Horst study included a small percentage of patients who had diabetes. The group agreed that although the definition of hyperglycaemia varied across the studies, a blood glucose level above 11 mmol/litre was an internationally accepted threshold for diagnosing hyperglycaemia.

The group felt that although there was conflicting evidence, when taking into account the drawbacks of the MINAP data, there was no evidence to support using intensive insulin therapy in this group of patients. However, the group did acknowledge that the MINAP data reflected current practice in the UK and showed that many patients were not receiving any treatment for hyperglycaemia. It also recognised that the risk of adverse events associated with hyperglycaemia that is not managed appropriately was high, and it felt that a separate recommendation should be made to ensure that hyperglycaemia is managed using methods other than intensive insulin therapy. The group agreed a target blood glucose level of less than 11 mmol/litre because it was the upper limit of the target blood glucose level used in the included studies. The GDG did not set a minimum glucose level because this varied across the studies and the group wanted to avoid an arbitrary figure.

### 3.2.6 Recommendations and research recommendations for people with ACS and hyperglycaemia without a diagnosis of diabetes

**Recommendations**

**Recommendation 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.

**Recommendation 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.

**Research recommendations**

See appendix B for full details of the research recommendation.

**Research recommendation B1**

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

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

### 3.3.1 Review question

What risk factors are associated with the development of diabetes in people with hyperglycaemia in ACS?

### 3.3.2 Evidence review

This review question focused on identifying patients who are at high risk of progression to diabetes. The diagnosis of diabetes was specifically excluded as formal testing for diabetes will normally take place within primary care after the acute episode. Five prognostic studies were selected for this review question (Ishihara et al. 2006; Norhammar et al. 2002; Okosieme et al. 2008; Tenerz et al. 2003; Oswald and Yudkin 1987). Papers were excluded if they:

- focused on risk factors for other outcomes such as cardiovascular events and mortality
- focused on patients who had previously been diagnosed with diabetes, or
- did not provide a definition for hyperglycaemia

(for a full list of excluded papers, see appendix D).

Because GRADE has not been developed for use with prognostic studies, a modified approach was used in which the same criteria (limitations, inconsistency, imprecision and indirectness) were used to downgrade the quality of the evidence. Overall, the risk of bias was considered low because the included papers were prospective cohort studies looking at metabolic or biochemical predictors of diabetes. Therefore studies were started as high-quality evidence and were downgraded as appropriate.

**Table 7 Summary of included studies for adults with ACS who are at risk of diabetes**

| Author (year) | Testing for diabetes | Test used to assess blood glucose level | Definitions[a] | Location |
|---|---|---|---|---|
| Tenerz et al. (2003) | 3 months | Capillary whole blood | NGT: FBG < 6.1 mmol/litre, BG-2h < 7.8 mmol/litre<br>Diabetes: FBG ≥ 6.1 mmol/litre and/or BG-2h ≥ 11.1 mmol/litre<br>IGT: FBG < 6.1 mmol/litre, BG-2h 7.8–11.0 mmol/litre | Sweden |
| Norhammar et al. (2002) | 3 months | Capillary whole blood | NGT: FBG < 6.1 mmol/litre and BG-2h < 7.8 mmol/litre<br>Diabetes: FBG > 6.0 mmol/litre and/or BG-2h > 11.0 mmol/litre<br>IGT: FBG < 6.1 mmol/litre and BG-2h 7.8–11.0 mmol/litre | Sweden |
| Ishihara et al. (2006) | Discharge from hospital | Plasma glucose | NGT: FBG < 7.0 mmol/litre and BG-2h < 7.8 mmol/litre<br>Diabetes: FBG ≥ 7.0 mmol/litre and/or BG-2h ≥ 11.1 mmol/litre<br>IGT: FBG < 7.0 and BG-2h of 7.8–11.0 mmol/litre | Japan |
| Okosieme et al. (2008) | Discharge from hospital | Plasma glucose | NGT: FPG < 5.6 mmol/litre, BG-2h < 7.8 mmol/litre<br>Diabetes: BG-2h ≥ 11.1 mmol/litre, FPG ≥ 7.0 mmol/litre<br>IGT: BG-2h 7.8–11.0 mmol/litre, FPG 5.6–6.9 mmol/litre | UK |
| Oswald and Yudkin (1987) | At 7–10 days and at 3 months | Plasma glucose | Classified according to WHO (1980) – no specific details provided in paper | UK |

Abbreviations: BG-2h, 2-hour blood glucose level; FBG, fasting blood glucose; FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NGT, normal glucose tolerance.

[a] Data were treated as categorical unless otherwise stated in the GRADE table.

## Table 8 GRADE table summary for risk factors associated with diabetes

| Quality assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No. of patients | | Effect/Outcome | Length of follow-up | Quality[a] |
| No. of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | Total | Diabetes at follow-up | | | |
| **Prevalence of diabetes in patients with ACS and undiagnosed diabetes** | | | | | | | | | | | |
| 4 studies (Ishihara et al. 2006, Okosieme et al. 2008, Norhammar et al. 2002, Tenerz et al. 2003) | Prognostic | Serious[b] | No serious inconsistency | No serious indirectness | Serious[c] | No serious other considerations | 626 | 163 | The prevalence of diabetes[d] in patients with ACS and hyperglycaemia ranged from 25 to 27% | Up to 3 months after admission | LOW |
| **Short-term multivariate predictors of diabetes or impaired glucose tolerance** | | | | | | | | | | | |
| 1 study (Ishihara et al. 2006) | Prognostic | Serious[b] | No serious inconsistency | Serious[e] | Serious[c] | No serious other considerations | 200 | 53 | Short-term multivariate predictors of diabetes or impaired glucose tolerance at discharge included the following factors:<br>• fasting glucose (OR 5.00, 95% CI 1.97 to 12.50, p < 0.001), $HbA_{1c}$ (OR 5.76, 95% CI 1.50 to 22.16, p = 0.01)<br>• fasting insulin (OR 1.17, 95% CI 1.04 to 1.31, p = 0.007)<br>• time to angiography (OR 1.17, 95% CI 1.04 to 1.32, p = 0.01) | Discharge (up to 1 week after admission) | VERY LOW |

| Quality assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No. of patients | | Effect/Outcome | Length of follow-up | Quality[a] |
| No. of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | Total | Diabetes at follow-up | | | |
| 1 study (Ishihara et al. 2006) | Prognostic | Serious[b] | No serious inconsistency | Serious[e] | Serious[c] | No serious other considerations | 200 | 53 | Admission glucose was not a short-term predictor of diabetes or impaired glucose tolerance at discharge (OR 0.98, 95% CI 0.84 to 1.16, p = 0.85) | Discharge (up to 1 week after admission) | VERY LOW |
| **Short-term use of predictors to diagnose diabetes** | | | | | | | | | | | |
| 2 studies (Ishihara et al. 2006, Okosieme et al. 2008) | Prognostic | Serious[b] | No serious inconsistency | No serious indirectness | Serious[c] | No serious other considerations | 340 | 91 | The use of admission blood glucose > 7.8 mmol/litre to diagnose diabetes at discharge was associated with the following diagnostic statistics:<br>sensitivity values were 72% (95% CI 58 to 83%) and 66% (95% CI 49 to 80%)<br>specificity values were 45% (95% CI 37 to 53%) and 83% (95% CI 75 to 90%)<br>PPV 32% (95% CI 24 to 41%) and 60% (95% CI 43 to 74%)<br>NPV 81% (95% CI 71 to 89%) and 87% (95% CI 78 to 93%) | Discharge (up to 1 week after admission) | LOW |
| 1 study (Okosieme et al. 2008) | Prognostic | Serious[b] | No serious inconsistency | No serious indirectness | Serious[c] | No serious other considerations | 140 | 38 | The use of fasting plasma glucose ≥ 5.6 mmol/litre to diagnose diabetes at discharge was associated with the following diagnostic statistics:<br>sensitivity = 82% (95% CI 66 to 92%), specificity = 65% (95% CI 55 to 74%), PPV = 47% (95% CI 34 to 59%), AUC = 0.83 (p < 0.001) | Discharge (up to 1 week after admission) | LOW |

| Quality assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No. of patients | | Effect/Outcome | Length of follow-up | Quality[a] |
| No. of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | Total | Diabetes at follow-up | | | |
| 1 study (Okosieme et al. 2008) | Prognostic | Serious[b] | No serious inconsistency | No serious indirectness | Serious[c] | No serious other considerations | 140 | 38 | The use of admission plasma glucose ≥ 7.8 mmol/litre or FPG ≥ 5.6 mmol/litre to diagnose diabetes at discharge was associated with the following diagnostic statistics[f]:<br>sensitivity = 90%, specificity = 57%, PPV = 44%, AUC = 0.84 (p < 0.001) | Discharge (up to 1 week after admission) | LOW |
| 1 study Okosieme et al. 2008) | Prognostic | Serious[b] | No serious inconsistency | No serious indirectness | Serious[c] | No serious other considerations | 140 | 38 | The optimal cut-off point for admission blood glucose was 7.7 mmol/litre (providing a sensitivity of 66%, specificity of 82%[f]) to identify diabetes at discharge | Discharge (up to 1 week after admission) | LOW |
| 1 study, Okosieme et al. 2008) | Prognostic | Serious[b] | No serious inconsistency | No serious indirectness | Serious[c] | No serious other considerations | 140 | 38 | The optimal cut-off point for using fasting blood glucose was 5.8 mmol/litre (providing a sensitivity of 69%, specificity of 77%[f]) to identify diabetes at discharge | Discharge (up to 1 week after admission) | LOW |
| **Longer-term multivariate predictors of diabetes [g]** | | | | | | | | | | | |
| 1 study (Norhammar et al. 2002) | Prognostic | No serious limitations | No serious inconsistency | Serious[i] | Serious[c] | No serious other considerations | 142 | 36 | Fasting blood glucose on day 4 (OR 2.97, 95% CI 1.55 to 6.40, p = 0.002 for increase of 1 mmol in blood glucose) was the only statistically significant predictor of diabetes 3 months after admission[h] | 3 months | LOW |

| Quality assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No. of patients | | Effect/Outcome | Length of follow-up | Quality[a] |
| No. of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | Total | Diabetes at follow-up | | | |
| **Longer-term multivariate predictors of diabetes or impaired glucose tolerance[g]** | | | | | | | | | | | |
| 2 studies (Tenerz et al. 2003, Norhammar et al. 2002) | Prognostic | No serious limitations | No serious inconsistency | Serious[e] | Serious[c] | No serious other considerations | 286 | 72 | Long-term multivariate predictors of diabetes or impaired glucose tolerance included the following factors:<br>Inpatient oral glucose tolerance test including blood glucose measurement after 60 minutes (OR for 1 mmol/litre increase in BG-60 was 1.38, 95% CI 1.16 to 1.64)<br>Fasting blood glucose on day 4 (OR 1.90, 95% CI 1.05 to 3.69, p = 0.04 for increase of 1 mmol in blood glucose)<br>$HbA_{1c}$ (for increase in 1%) (OR 2.58, 95% CI 1.17 to 6.09, p = 0.02) | 3 months | LOW |
| **Longer-term use of predictors to diagnose diabetes** | | | | | | | | | | | |
| 1 study (Norhammar et al. 2002) | Prognostic | No serious limitations | No serious inconsistency | Serious[i] | Serious[c] | No serious other considerations | 142 | 36 | A fasting blood glucose of > 5.3 mmol/litre on day 4 (discharge) was able to predict newly detected diabetes at 3 months (providing a sensitivity of 80%, specificity of 57%[f]) and AUC value was 0.710 (p < 0.0001) | 3 months | LOW |
| 1 study (Oswald and Yudkin 1987) | Prognostic | Serious[j] | No serious inconsistency | Serious[i] | Serious[c] | No serious other considerations | 110 | 9 | An admission plasma glucose > 11 mmol/litre was able to predict diabetes at 3 months with a sensitivity of 33% (95% CI 3 to 64%) and a specificity of 91% (95% CI 85 to 97%) | 3 months | VERY LOW |

| Quality assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No. of patients | | Effect/Outcome | Length of follow-up | Quality[a] |
| No. of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | Total | Diabetes at follow-up | | | |
| 1 study Oswald and Yudkin 1987 | Prognostic | Serious[j] | No serious inconsistency | Serious[i] | Serious[c] | No serious other considerations | 110 | 9 | A $HbA_{1c}$ > 7.8% was able to predict diabetes at 3 months with a sensitivity of 67% (95% CI 36 to 97%) and a specificity of 99% (95% CI 97 to 100%) | 3 months | VERY LOW |

[a] Studies were started with a high-quality rating and were downgraded as appropriate.

[b] Period of follow-up may be insufficient to provide an accurate diagnosis of diabetes.

[c] Where reported the majority of 95% confidence intervals are wide, but because imprecision cannot be assessed in diagnostic and prognostic studies it has been assumed that imprecision exists for all outcomes and this criteria has been downgraded.

[d] Using either fasting blood glucose or 2-h glucose criteria to diagnose diabetes.

[e] Outcome is diagnosis of either diabetes or impaired glucose tolerance (not diabetes alone).

[f] 95% confidence intervals are not reported for diagnostic statistics.

[g] Predictor was assessed as a continuous variable.

[h] Independent predictors of newly detected diabetes after 3 months were BMI and $HbA_{1c}$ at admission. When entering fasting blood glucose concentration on day 4 in the analysis, this parameter was the only remaining independent predictor of diabetes.

[g] Thresholds used for the diagnosis of diabetes differ to current thresholds.

[h] Patients with high $HbA_{1c}$ levels were more likely to be tested for diabetes at follow-up.

Abbreviations: APG, admission plasma glucose ; AUC, area under the curve; 95% CI, 95% confidence interval; FPG, fasting plasma glucose ; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value.

See appendix E for the evidence tables in full.

### 3.3.3 Evidence statements

For details of how the evidence is graded, see 'The guidelines manual'.

*3.3.3.1* *Low-quality evidence from four prognostic studies of 626 patients showed that the prevalence of diabetes in patients with hyperglycaemia and ACS ranged from 25% to 27% after up to 3 months follow-up.*

*3.3.3.2* *Very low-quality evidence from one study of 200 patients showed that fasting glucose (odds ratio [OR] 5.00, 95% CI 1.97 to 12.50), $HbA_{1c}$ (OR 5.76, 95% CI 1.50 to 22.16), fasting insulin (OR 1.17, 95% CI 1.04 to 1.31) and time to angiography (OR 1.17, 95% CI 1.04 to 1.32) significantly predicted the development of diabetes or impaired glucose tolerance at discharge.*

This study was conducted in Japan.

*3.3.3.3* *Very low-quality evidence from one study of 200 patients showed that admission glucose did not significantly predict diabetes or impaired glucose tolerance at discharge.*

This study was conducted in Japan.

*3.3.3.4* *Low-quality evidence from two studies of 340 patients showed that an admission glucose above 7.8 mmol/litre predicted diabetes at discharge (sensitivity 72% [95% CI 58 to 83%] and 66% [95% CI 49 to 80%], specificity 45% [95% CI 37 to 53%] and 83% [95% CI 75 to 90%], positive predictive value [PPV] 32% [95% CI 24 to 41%] and 60% [95% CI 43 to 74%], NPV 81% [95% CI 71 to 89%] and 87% [95% CI 78 to 93%]).*

One study was conducted in Japan, the other in the UK.

*3.3.3.5* *Low-quality evidence from one study of 140 patients showed that a fasting blood glucose of 5.6 mmol/litre or more predicted diabetes at discharge (sensitivity 82% [95% CI 66 to 92%], specificity 65%*

*[95% CI 55 to 74%], PPV 47% [95% CI 34 to 59%], area under the curve 0.83 [p < 0.001]).*

This study was conducted in the UK.

3.3.3.6 *Low-quality evidence from one study of 140 patients showed that an admission plasma glucose of 7.8 mmol/litre or more, or fasting blood glucose of 5.6 mmol/litre or more predicted diabetes at discharge (sensitivity 90%, specificity 57%, PPV 44%, area under the curve 0.84 [p < 0.001]).*

This study was conducted in the UK.

3.3.3.7 *Low-quality evidence from one study of 140 patients showed that the optimal cut-off point for admission blood glucose was 7.7 mmol/litre (sensitivity 66%, specificity 82%) to predict diabetes at discharge.*

This study was conducted in the UK.

3.3.3.8 *Low-quality evidence from one study of 140 patients showed that the optimal cut-off point for fasting blood glucose was 5.8 mmol/litre (sensitivity 69%, specificity 77%) to predict diabetes at discharge.*

This study was conducted in the UK.

3.3.3.9 *Low-quality evidence from one study of 142 patients showed that fasting blood glucose on day 4 was a statistically significant predictor of diabetes 3 months after admission (OR 2.97, 95% CI 1.55 to 6.40, p = 0.002 for an increase of 1 mmol in blood glucose).*

This study was conducted in Sweden.

3.3.3.10 *Low-quality evidence from two studies of 286 patients showed that an inpatient oral glucose tolerance test including BG-60 (OR 1.38 for 1 mmol/litre, 95% CI 1.16 to 1.64), fasting blood glucose on day 4 (OR 1.90, 95% CI 1.05 to 3.69 for an increase of 1 mmol in blood glucose) and $HbA_{1c}$ (OR 2.58 for 1 mmol/litre increase, 95%*

*CI 1.17 to 6.09) were all statistically significant predictors of diabetes or impaired glucose tolerance at 3-month follow-up.*

These studies were both conducted in Sweden.

3.3.3.11 *Low-quality evidence from one study of 142 patients showed that a fasting blood glucose above 5.3 mmol/litre on day 4 predicted diabetes at 3 months with a sensitivity of 80%, specificity of 57% and area under the curve of 0.710.*

This study was conducted in Sweden.

3.3.3.12 *Very low-quality evidence from one study of 110 patients showed that an admission plasma glucose above 11 mmol/litre predicted diabetes at 3 months with a sensitivity of 33% (95% CI 3 to 64%) and a specificity of 91% (95% CI 85 to 97%).*

This study was conducted in the UK.

3.3.3.13 *Very low-quality evidence from one study of 110 patients showed that a $HbA_{1c}$ above7.8% predicted diabetes at 3 months with a sensitivity of 67% (95 CI 36 to 97%) and specificity of 99% (95% CI 97 to 100%).*

This study was conducted in the UK.

### 3.3.4 Health economic assessment

No health economic analysis was conducted for this question.

### 3.3.5 Evidence to recommendations

The GDG agreed that a prognostic research design was appropriate to answer this review question. GRADE has not been developed to be used with prognostic studies, so a modified approach was used. The GDG felt that studies should start with a high quality rating and should be downgraded as appropriate.

The evidence showed that both fasting blood glucose and $HbA_{1c}$ could be used to predict diabetes at follow-up. However, there was not enough evidence to support a recommendation for a specific threshold for either test. The group agreed that patients with high $HbA_{1c}$ levels and fasting blood glucose on discharge were at higher risk of developing diabetes, therefore these tests should be routinely used in practice. From the evidence, the group also felt that patients with low fasting glucose and/or low $HbA_{1c}$ would be less likely to develop diabetes, so testing using an oral glucose tolerance test would not be as important for this group of patients at this stage. The GDG also discussed the fact that blood glucose levels would be distorted as a result of the acute event. Therefore, test results on day 4 may be more reliable than using test results on admission to identify patients who are at higher risk of a diagnosis of diabetes. It was agreed that formal testing and diagnosis of diabetes will normally take place following referral to primary care after the acute episode.

### 3.3.6 Recommendations and research recommendations for risk of diabetes

**Recommendations**

**Recommendation 1.1.3**

Offer all patients with hyperglycaemia after ACS and without known diabetes tests for:

- $HbA_{1c}$ levels before discharge **and**
- fasting blood glucose levels no earlier than 4 days after the onset of ACS.

These tests should not delay discharge.

**Recommendation 1.1.4**

Do not routinely offer oral glucose tolerance tests to patients with hyperglycaemia after ACS and without known diabetes if $HbA_{1c}$ and fasting blood glucose levels are within the normal range.

**Research recommendations**

No research recommendations have been made for this question. See appendix B for full details of the research recommendation.

## *3.4 Patient information*

### 3.4.1 Review question

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

### 3.4.2 Evidence review

This review question focused on the information and support needs of patients who have been identified as being at high risk of developing diabetes before formal diagnostic investigations in primary care. Although all study designs were considered, no evidence was found for this review question. Papers were excluded if:

- they included patients with a previous diagnosis of diabetes, unless it focused on their experiences before diagnosis, and
- they focused on patient information or support needs for patients with ACS or hyperglycaemia, but not both (for a full list of excluded studies see appendix D).

GRADE was not used for this question because there was no evidence. Instead, the GDG was presented with a summary table of related NICE guidance and a brief overview of the type of patient information that has been recommended for patients with either ACS (specifically those who have had a myocardial infarction and those with unstable angina) or a diagnosis of type 2 diabetes. The group was asked to consider what information should be provided in addition to what has already been recommended for these patients.

## Table 9 Summary table for patient information

| | | | Type of patient information (This is only a summary of the advice that should be provided, not full recommendations) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Guideline** | **Year of publication** | **Target group** | **Dietary** | **Physical activity** | **Weight management** | **Smoking cessation** | **Alcohol** | **Cardiac rehabilitation** | **Other (specify)** |
| MI: secondary prevention (NICE clinical guideline 48) | 2007 | People who have had an MI | Including increased omega 3, eating a Mediterranean style diet and general healthy eating advice | Including regular physical activity for 20–30 minutes a day | Include advice and support to achieve and maintain a healthy weight for overweight or obese patients (see 'Obesity', NICE clinical guideline 43 for details) | Include advice to quit and assistance from smoking cessation service for all patients who smoke and referral to intensive support service for those expressing desire to quit | Advise to keep within safe limits of consumption | Include cardiac rehabilitation programme with exercise component, health education and stress management components | N/A |
| Unstable angina and NSTEMI (NICE clinical guideline 94) | 2010 | People with unstable angina<br>Advice should be given before discharge | Lifestyle changes in line with 'MI: secondary prevention' | Lifestyle changes in line with 'MI: secondary prevention' | Lifestyle changes in line with 'MI: secondary prevention' | All patients who smoke should be advised to quit and be offered support and advice, and referral to intensive support service | Lifestyle changes in line with 'MI: secondary prevention' | This should be in line with 'MI: secondary prevention' | Diagnosis and arrangement for follow-up, management of cardiovascular risk factors and drug therapy for secondary prevention |

| | | | Type of patient information (This is only a summary of the advice that should be provided, not full recommendations) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Guideline** | **Year of publication** | **Target group** | **Dietary** | **Physical activity** | **Weight management** | **Smoking cessation** | **Alcohol** | **Cardiac rehabilitation** | **Other (specify)** |
| Type 2 diabetes (NICE clinical guideline 87) | 2009 | People with diabetes | Including high-fibre, low glycaemic index sources of carbohydrate in the diet, such as fruit, vegetables, whole grains and pulses; include low-fat dairy products and oily fish; and control the intake of foods containing saturated and trans fatty acids and discouraging the use of foods marketed specifically for people with diabetes | Integrate dietary advice with a personalised diabetes management plan, including other aspects of lifestyle modification, such as increasing physical activity and losing weight | Target an initial body weight loss of 5–10% in people who are overweight | Smoking cessation is not addressed in this guideline | Individual advice about carbohydrate and alcohol intake, and meal patterns | N/A | N/A |

### 3.4.3 Evidence statements

No evidence was identified on patient information needs and support for people with ACS and hyperglycaemia without a previous diagnosis of diabetes.

### 3.4.4 Health economic assessment

No health economic analysis was conducted for this question.

### 3.4.5 Evidence to recommendations

The GDG acknowledged the lack of evidence to answer this review question for patients with ACS and hyperglycaemia and who have no previous diagnosis of diabetes. The group agreed that the lifestyle advice that would be given as part of ACS management was the most important factor in terms of reducing the risk of progressing to diabetes.

The group felt that patients should also be given information about their overall risk of developing or not developing diabetes at a later stage. In particular they recognised that although some patients will have consistently high blood glucose levels and may progress to type 2 diabetes, blood glucose levels in other patients may normalise. There may be variation in terms of which patients are currently provided with follow-up, so the GDG decided that monitoring of this high-risk group would be improved by secondary care staff informing the GP that a patient needs routine follow-up. Specifically, it felt that follow-up should include a biochemical test to ensure that diabetes status is assessed.

The evidence reviewed did not identify any subgroups based on ethnicity that were associated with poorer outcomes when patients were treated with intensive insulin therapy. However, the GDG discussed the fact that some ethnic groups may have a lower index of suspicion for diabetes and others, such as people of south Asian descent, may be genetically predisposed to developing diabetes. However, it was felt that experiencing an ACS such as an acute myocardial infarction would override any biological predisposition to developing diabetes and routine follow-up would allow these groups to be assessed appropriately.

### 3.4.6 Recommendations and research recommendations for patient information

**Recommendations**

**Recommendation 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).

**Recommendation 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.

**Recommendation 1.1.7**

Inform GPs that they should offer at least annual monitoring of $HbA_{1c}$ and fasting blood glucose levels to people without known diabetes who have had hyperglycaemia after an ACS.

**Research recommendations**

No research recommendations have been made for this question. See appendix B for full details of the research recommendations.

# 4 Notes on the scope of the guideline

NICE guidelines are developed in accordance with a scope that defines what the guideline will and will not cover. The scope of this guideline is given in appendix C.

# 5 Implementation

NICE has developed tools to help organisations implement this guidance (see www.nice.org.uk/guidance/CG130).

# 6 Other versions of this guideline

## *6.1 NICE pathway*

The recommendations from this guideline have been incorporated into a NICE pathway which is available from http://pathways.nice.org.uk/pathways/hyperglycaemia-in-acute-coronary-syndromes

## *6.2 'Understanding NICE guidance'*

A summary for patients and carers ('Understanding NICE guidance') is available from www.nice.org.uk/guidance/CG130/PublicInfo

For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk (quote reference number N2676).

We encourage NHS and voluntary sector organisations to use text from this booklet in their own information about hyperglycaemia in acute coronary syndromes.

# 7 Related NICE guidance

**Published**

- Diabetes in adults. NICE quality standard (2011). Available from www.nice.org.uk/guidance/qualitystandards/diabetesinadults/diabetesinadultsqualitystandard
- Alcohol-use disorders – preventing harmful drinking. NICE public health guidance 24 (2010). Available from www.nice.org.uk/guidance/PH24
- Liraglutide for the treatment of type 2 diabetes mellitus. NICE technology appraisal guidance 203 (2010). Available from www.nice.org.uk/guidance/TA203
- Chronic heart failure. NICE clinical guideline 108 (2010). Available from www.nice.org.uk/guidance/CG108
- Chest pain of recent onset. NICE clinical guideline 95 (2010). Available from www.nice.org.uk/guidance/CG95
- Unstable angina and NSTEMI. NICE clinical guideline 94 (2010). Available from www.nice.org.uk/guidance/CG94
- Type 2 diabetes (partial update of CG 66). NICE clinical guideline 87 (2009). Available from www.nice.org.uk/guidance/CG87
- Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention. NICE technology appraisal guidance 182 (2009). Available from www.nice.org.uk/guidance/TA182
- Smoking cessation services. NICE public health guidance 10 (2008). Available from www.nice.org.uk/guidance/PH10
- Diabetes in pregnancy. NICE clinical guideline 63 (2008). Available from www.nice.org.uk/guidance/CG63
- Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus (review). NICE technology appraisal guidance 151 (2008). Available from www.nice.org.uk/guidance/TA151

- MI: secondary prevention. NICE clinical guideline 48 (2007). Available from www.nice.org.uk/guidance/CG48
- Four commonly used methods to increase physical activity. NICE public health guidance 2 (2006). Available from www.nice.org.uk/guidance/PH2
- Brief interventions and referral for smoking cessation. NICE public health guidance 1 (2006). Available from www.nice.org.uk/guidance/PH1
- Obesity. NICE clinical guideline 43 (2006). Available from www.nice.org.uk/guidance/CG43
- Type 1 diabetes in children, young people and adults. NICE clinical guideline 15 (2004). Available from www.nice.org.uk/guidance/CG15
- Type 2 diabetes: prevention and management of foot problems. NICE clinical guideline 10 (2004). Available from www.nice.org.uk/guidance/CG10
- Myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction. NICE technology appraisal guidance 73 (2003). Available from www.nice.org.uk/guidance/TA73
- Guidance on the use of long acting insulin analogues for the treatment of diabetes – insulin glargine. NICE technology appraisal guidance 53 (2002). Available from www.nice.org.uk/guidance/TA53
- Guidance on the use of drugs for early thrombolysis in the treatment of acute myocardial infarction. NICE technology appraisal guidance 52 (2002). Available from www.nice.org.uk/guidance/TA52
- Guidance on the use of glycoprotein IIb/IIIa inhibitors in the treatment of acute coronary syndromes. NICE technology appraisal guidance 47 (2002). Available from www.nice.org.uk/guidance/TA47 (partially updated by NICE clinical guideline 94)
- Alcohol dependence and harmful alcohol use. NICE clinical guideline 115 (2011). Available from www.nice.org.uk/guidance/CG115

**Under development**

NICE is developing the following guidance (details available from www.nice.org.uk):

- Ticagrelor for the treatment of acute coronary syndromes. NICE technology appraisal. Publication expected October 2011.
- Type 2 diabetes-preventing the progression from pre-diabetes. NICE public health guidance. Publication expected May 2012
- Long-acting exenatide for the second-line (dual therapy) or third-line (triple therapy) treatment of type 2 diabetes. NICE technology appraisal. Publication expected February 2012.
- Buccal insulin for the management of type 1 diabetes. NICE technology appraisal. Publication date to be confirmed.

# 8 Updating the guideline

NICE clinical guidelines are updated so that recommendations take into account important new information. New evidence is checked 3 years after publication, and healthcare professionals and patients are asked for their views; we use this information to decide whether all or part of a guideline needs updating. If important new evidence is published at other times, we may decide to do a more rapid update of some recommendations. Please see our website for information about updating the guideline.

# 9 References

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CREATE-ECLA (2005) Effect of glucose-insulin-potassium infusion on mortality in patients with acute ST-segment elevation myocardial infarction: the CREATE-ECLA randomized controlled trial. Journal of the American Medical Association 293: 437–47

Ishihara M, Inoue I, Kawagoe T et al. (2006) Is admission hyperglycaemia in non-diabetic patients with acute myocardial infarction a surrogate for previously undiagnosed abnormal glucose tolerance? European Heart Journal 27: 2413–9

Malmberg K, Rydén L, Wedel H et al. (2005) Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. European heart journal 26: 650–61

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Norhammar A, Tenerz A, Nilsson G et al. (2002) Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: A prospective study. Lancet 359: 2140–4

Okosieme OE, Peter R, Usman M et al. (2008) Can admission and fasting glucose reliably identify undiagnosed diabetes in patients with acute coronary syndrome? Diabetes Care 31: 1955–9

Oswald GA, Yudkin JS (1987) Hyperglycaemia following acute myocardial infarction: The contribution of undiagnosed diabetes. Diabetic Medicine 4: 68–70

Tenerz A, Norhammar A, Silveira A et al. (2003) Diabetes, insulin resistance, and the metabolic syndrome in patients with acute myocardial infarction without previously known diabetes. Diabetes Care 26: 2770–6

van der Horst ICC, Zijlstra F, van't Hof AWJ et al. (2003) Glucose-insulin-potassium infusion in patients treated with primary angioplasty for acute myocardial infarction: The glucose-insulin-potassium study: A randomized trial. Journal of the American College of Cardiology 42: 784–91

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# 10 Glossary and abbreviations

## *10.1 Glossary*

**Acute coronary syndrome (ACS)**

Acute coronary syndromes (ACS) encompass a spectrum of unstable coronary artery disease, ranging from unstable angina to transmural myocardial infarction.

**Congestive heart failure**

The inability of the heart to supply sufficient blood flow to meet the body's needs.

**Hypergylcaemia**

A blood glucose level above 11 mmol/litre.

**Hypoglycaemia**

A blood glucose level below the normal range (usually less than 4 mmol/litre).

**Intensive insulin therapy**

An intravenous infusion of insulin and glucose, with or without potassium.

**Killip class**

A measure of severity of congestive heart failure, ranging from 1 to 4. Class 1 indicates no clinical signs of heart failure, and classes 2 to 4 indicate increasing risk of heart failure.

**Normoglycaemia**

A blood glucose level within the normal range.

**Reinfarction**

A subsequent episode of acute myocardial infarction.

Please see the NICE glossary (www.nice.org.uk/website/glossary/glossary.jsp) for an explanation of terms not described above.

## *10.2 Abbreviations*

| Abbreviation | Term |
|---|---|
| $HbA_{1c}$ | Glycated haemoglobin |
| STEMI | ST–segment-elevation myocardial infarction |
| NSTEMI | Non-ST–segment-elevation myocardial infarction |

# Appendix A Contributors and declarations of interests

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The Guideline Review Panel is an independent panel that oversees the development of the guideline and takes responsibility for monitoring adherence to NICE guideline development processes. In particular, the panel ensures that stakeholder comments have been adequately considered and responded to. The panel includes members from the following perspectives: primary care, secondary care, lay, public health and industry.

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## *Declarations of interests*

| GDG Member | Interest declared | Type of interest | Decision |
|---|---|---|---|
| Simon Corbett | Speaker fees for Pfizer (atorvastatin) and Boston Scientific, £700 and £800 | Personal pecuniary, non-specific | Declare and can participate in discussions on all topics because the work was not specific to hyperglycaemia in ACS |
| | Advisory board attendance for Servier (ivabradine) and Boston Scientific £750 and £750 | Personal pecuniary, non-specific | Declare and can participate in discussions on all topics because the work was not specific to hyperglycaemia in ACS |
| Lesley Mills | None declared | | |
| Philip Dyer | None declared | | |
| Bernard Clarke | None declared | | |
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| Sunil Angris | None declared | | |
| Ian Lewin | None declared | | |
| Steven Williams | None declared | | |

# Appendix B Research recommendation

The Guideline Development Group has made the following recommendation for research, based on its review of evidence, to improve NICE guidance and patient care in the future.

## B1 Optimal management of hyperglycaemia in ACS

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

**Why this is important**

Existing studies on the optimal management of hyperglycaemia in people who have ACS and diagnosed or previously undiagnosed diabetes are generally of poor quality.

It is recommended that a large randomised controlled trial is conducted for people with ACS and hyperglycaemia (blood glucose 11 mmol/litre and over) stratified by NSTEMI and STEMI and by known diabetes and without a previous diagnosis of diabetes.

The interventions for the trial should be intravenous insulin or subcutaneous insulin administered within 4 hours of presentation to hospital. The aim is to achieve blood glucose between 6 and 11 mmol/litre for at least 24 hours. The comparator should be standard care.

## Appendix C Guideline scope

# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

# SCOPE

## 1 Guideline title

Hyperglycaemia in acute coronary syndromes: management of hyperglycaemia in people with acute coronary syndromes

### *1.1 Short title*

Hyperglycaemia in acute coronary syndromes

## 2 The remit

The Department of Health has asked NICE: ‘to produce a short clinical guideline on the management of hyperglycaemia in acute coronary syndrome in patients both with and without diagnosed diabetes mellitus'.

## 3 Clinical need for the guideline

### *3.1 Epidemiology*

Acute coronary syndromes (ACS) encompass a spectrum of unstable coronary artery disease from unstable angina to transmural myocardial infarction. All forms begin with an inflamed and complicated fatty deposit (known as an atheromatous plaque) in a blood vessel, and blood clots forming on the plaque. The principles behind the presentation, investigation and management of these syndromes are similar with important distinctions depending on the category of acute coronary syndrome.

Hyperglycaemia is common in patients when they are admitted to hospital with ACS. Recent studies found that approximately 65% of patients with acute

myocardial infarction (heart attack) who were not known to have diabetes had impaired glucose regulation when given a glucose tolerance test.

For patients both with and without diabetes mellitus, hyperglycaemia on admission is a powerful predictor of poorer survival and increased risk of complications while in hospital. Despite this, hyperglycaemia remains underappreciated as a risk factor in acute coronary syndromes and it is frequently untreated.

Persistently elevated blood glucose levels during acute myocardial infarction have been shown to be associated with increased in-hospital mortality, and to be a better predictor of outcome than admission blood glucose.

## *3.2 Current practice*

Currently, the management of hyperglycaemia in people with acute coronary syndromes is inconsistent across the UK, whether or not the person has diagnosed diabetes

The Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice recommend that:

- In people who present with an acute cardiovascular event, fasting glucose should be measured at least once, or an oral glucose tolerance test performed, during their hospital stay
- Fasting glucose should be measured during the acute phase of the illness. If there is evidence of impaired fasting glucose (more than 6.0 mmol/litre but less than 7.0 mmol/litre) or an indication of diabetes (more than 7.0 mmol/litre) fasting glucose should be measured twice (or an oral glucose tolerance test performed once) between 8 and 12 weeks after discharge from hospital.

The SIGN guidelines on acute coronary syndromes recommend that patients with clinical myocardial infarction and diabetes or marked hyperglycaemia (more than 11 mmol/litre) should be given immediate intensive blood glucose control. This should be continued for at least 24 hours. The European Society

of Cardiology also recommends that patients with acute myocardial infarction and diabetes should be given tight glucometabolic control.

There is currently no relevant national guidance for England, Wales and Northern Ireland on the management of hyperglycaemia in people with acute coronary syndromes.

# 4 The guideline

The guideline development process is described in detail on the NICE website (see section 6, 'Further information').

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

The areas that will be addressed by the guideline are described in the following sections.

## *4.1 Population*

### 4.1.1 Groups that will be covered

- Adults with acute coronary syndromes and hyperglycaemia with a diagnosis of diabetes.
- Adults with acute coronary syndromes and hyperglycaemia without a diagnosis of diabetes.
- Subgroups who are at higher risk of mortality and poorer outcomes associated with acute coronary syndrome will be considered as appropriate.

### 4.1.2 Groups that will not be covered

- Adults with hyperglycaemia who do not have acute coronary syndromes.
- Adults with acute coronary syndromes who do not have hyperglycaemia.

## *4.2 Healthcare setting*

Secondary and tertiary care.

## *4.3 Clinical management*

### 4.3.1 Key clinical issues that will be covered

- Threshold values of blood glucose levels for intervention.
- Inpatient glucometabolic management (glucose, potassium and insulin) of hyperglycaemia in patients with acute coronary syndrome, who have diagnosed diabetes mellitus.
- Inpatient glucometabolic management (glucose, potassium and insulin) of hyperglycaemia in patients with acute coronary syndrome, who do not have diagnosed diabetes mellitus.
- Timing and frequency of blood glucose level measures for monitoring purposes in hospital.
- Referral for subsequent investigation to confirm possible diabetes in patients without an existing diagnosis of diabetes.

### 4.3.2 Clinical issues that will not be covered

- Diagnosis of diabetes mellitus.
- Management of diabetes mellitus.
- Diagnosis of acute coronary syndromes.
- Management of acute coronary syndromes.
- Types of medical devices used to measure hyperglycaemia.
- Long-term management of hyperglycaemia and support beyond the acute phase.

## *4.4 Main outcomes*

- All-cause mortality.
- Cardiovascular mortality.
- Cardiovascular events such as non-fatal reinfarction, heart failure and stroke.
- Measures and control of blood glucose levels.

- Health related quality of life.
- Adverse events associated with metabolic management of hyperglycaemia, including hypoglycaemia and hypokalaemia.
- Resource use and costs, such as length of hospital stay.

## *4.5 Economic aspects*

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually be only from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in 'The guidelines manual' (see ‘Further information’).

The key health economic question is the cost effectiveness of intensive glucometabolic management of hyperglycaemia in inpatients with acute coronary syndromes and hyperglycaemia with or without diabetes. The full economic analysis will be developed in conjunction with the Clinical Review Group and the Guideline Development Group.

## *4.6 Status*

### 4.6.1 Scope

This is the final scope.

### 4.6.2 Timing

The development of the guideline recommendations will begin in November 2010.

# 5 Related NICE guidance

## *5.1 Published guidance*

### 5.1.1 Other related NICE guidance

- Liraglutide for the treatment of type 2 diabetes mellitus. NICE technology appraisal guidance 203 (2010). Available from www.nice.org.uk/guidance/TA203
- Chronic heart failure. NICE clinical guideline 108 (2010). Available from www.nice.org.uk/guidance/CG108
- Chest pain of recent onset. NICE clinical guideline 95 (2010). Available from www.nice.org.uk/guidance/CG95
- Unstable angina and NSTEMI. NICE clinical guideline 94 (2010). Available from www.nice.org.uk/guidance/CG94
- Type 2 diabetes (partial update of CG 66). NICE clinical guideline 87 (2009). Available from www.nice.org.uk/guidance/CG87
- Diabetes in pregnancy. NICE clinical guideline 63 (2008). Available from www.nice.org.uk/guidance/CG63
- Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention. NICE technology appraisal guidance 182 (2009). Available from www.nice.org.uk/guidance/TA182
- Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus (review). NICE technology appraisal guidance 151 (2008). Available from www.nice.org.uk/guidance/TA151
- MI: secondary prevention. NICE clinical guideline 48 (2007). Available from www.nice.org.uk/guidance/CG48
- Type 1 diabetes in children, young people and adults. NICE clinical guideline 15 (2004). Available from www.nice.org.uk/guidance/CG15
- Type 2 diabetes: prevention and management of foot problems. NICE clinical guideline 10 (2004). Available from www.nice.org.uk/guidance/CG10

- Myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction. NICE technology appraisal guidance 73 (2003). Available from www.nice.org.uk/guidance/TA73
- Guidance on the use of long acting insulin analogues for the treatment of diabetes – insulin glargine. NICE technology appraisal guidance 53 (2002). Available from www.nice.org.uk/guidance/TA53
- Guidance on the use of drugs for early thrombolysis in the treatment of acute myocardial infarction. NICE technology appraisal guidance 52 (2002). Available from www.nice.org.uk/guidance/TA52
- Guidance on the use of glycoprotein IIb/IIIa inhibitors in the treatment of acute coronary syndromes. NICE technology appraisal guidance 47 (2002). Available from www.nice.org.uk/guidance/TA47

### *5.2 Guidance under development*

NICE is currently developing the following related guidance (details available from the NICE website):

- Ticagrelor for the treatment of acute coronary syndromes. NICE technology appraisal guidance. Publication expected July 2011.
- Long-acting exenatide for the second-line (dual therapy) or third-line (triple therapy) treatment of type 2 diabetes. NICE technology appraisal guidance. Publication date to be confirmed.
- Buccal insulin for the management of type 1 diabetes. NICE technology appraisal guidance. Publication date to be confirmed.

## 6 Further information

Information on the guideline development process is provided in:

- 'How NICE clinical guidelines are developed: an overview for stakeholders the public and the NHS'
- 'The guidelines manual'.

These are available from the NICE website (www.nice.org.uk/GuidelinesManual). Information on the progress of the guideline will also be available from the NICE website

# Appendix D How this guideline was developed

This guideline was developed in accordance with the process for short clinical guidelines set out in 'The guidelines manual' (2009) (see www.nice.org.uk/GuidelinesManual). There is more information about how NICE clinical guidelines are developed on the NICE website (www.nice.org.uk/HowWeWork). A booklet, 'How NICE clinical guidelines are developed: an overview for stakeholders, the public and the NHS' (fourth edition, published 2009), is available from NICE publications (phone 0845 003 7783 or email publications@nice.org.uk and quote reference N1739).

## *Search strategies*

The evidence reviews used to develop the guideline recommendations were underpinned by systematic literature searches, following the methods described in 'The guidelines manual' (2009). The aim of the systematic searches was to comprehensively identify the published evidence to answer the review questions developed by the Guideline Development Group and Short Clinical Guidelines Technical Team.

The search strategies for the review questions were developed by the Information Services Team with advice from the Short Clinical Guidelines Technical Team. Structured questions were developed using the PICO (population, intervention, comparison, outcome) model and translated into search strategies using subject heading and free text terms. The strategies were run across a number of databases with no date restrictions imposed on the searches.

The NHS Economic Evaluation Database (NHS EED) and the Health Economic Evaluations Database (HEED) were searched for economic evaluations. Search filters for economic evaluations and quality of life studies were used on bibliographic databases. There were no date restrictions imposed on the searches.

Guideline Development Group members were also asked to alert the Short Clinical Guidelines Technical Team to any additional evidence, published, unpublished or in press, that met the inclusion criteria.

The searches were undertaken between June 2010 and September 2010.

## *Scoping searches*

Scoping searches were undertaken in May 2010 using the following websites and databases (listed in alphabetical order); browsing or simple search strategies were employed. The search results were used to provide information for scope development and project planning.
The below is a list of the related guidance used in the scoping searches

| **Guidance/guidelines** | **Systematic reviews/economic evaluations** |
|---|---|
| American Diabetes Association<br>British Medical Association<br>Canadian Medical Association Infobase<br>Clinical Knowledge Summaries<br>Clinical Resource Efficiency Support Team (CREST)<br>Department of Health<br>Diabetes UK<br>Guidelines International Network (GIN)<br>National Guideline Clearinghouse (US)<br>National Health and Medical Research Council (Australia)<br>New Zealand Guidelines Group<br>NHS Evidence<br>Royal College of Physicians<br>Royal Pharmaceutical Society<br>SIGN<br>University of Warwick<br>World Health Organisation | Clinical Evidence<br>Cochrane Database of Systematic Reviews (CDSR)<br>Database of Abstracts of Reviews of Effects (DARE)<br>Health Economic Evaluations Database (HEED)<br>Health Technology Assessment database (HTA)<br>NHS Economic Evaluation Database (NHS EED)<br>NHS R&D Service Delivery and Organisation Programme<br>National Institute for Health Research Health Technology Assessment Programme (NIHR)<br>TRIP Database |

### *Main searches*

The following sources were searched for the topics presented in the sections below.

- Clinical Trials.gov
- Current Controlled Trials
- Cochrane Database of Systematic Reviews – CDSR (Wiley)
- Cochrane Central Register of Controlled Trials – CENTRAL (Wiley)
- Database of Abstracts of Reviews of Effects – DARE (CRD)
- Health Technology Assessment Database – HTA (CRD)
- CINAHL (EBSCO)
- EMBASE (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)
- National Research Register Archive
- UK Clinical Research Network

What is the optimal inpatient metabolic management of patients presenting with hyperglycaemia and acute coronary syndrome (ACS) who have diagnosed diabetes mellitus and hyperglycaemia?

The following sources were searched to answer questions relating to:

Databases searched:

- Cochrane Central Register of Controlled Trials (Wiley)
- CINAHL (NHS Evidence)
- Cochrane Database of Systematic Reviews (Wiley)
- Database of Abstracts of Reviews of Effects (CRD)
- Embase (OVID)
- Health Technology Assessment database (CRD)
- Medline (OVID)
- Medline In-Process (OVID)

The searches were conducted on 10 August 2010.

Medline 1950 to July Week 4 2010

The Medline search strategy is presented below. It was translated for use in all of the other databases. Where appropriate, search filters for systematic reviews and randomised controlled trials were appended to the search strategies to retrieve high quality papers.

1. exp Hyperglycemia/
2. hyperglycemi$.tw.
3. hyperglycaemi$.tw.
4. (high$ adj3 plasma$ glucose$).tw.
5. (high$ adj3 blood$ glucose$).tw
6. (impair$ adj3 glucose$ regulation$).tw.
7. (high$ adj3 blood$ sugar$).tw.
8. (impair$ adj3 blood$ sugar$ regulation$).tw.
9. or/1-8
10. Acute Coronary Syndrome/
11. (acute$ adj3 coronary$ syndrome$).tw.
12. acs.tw.
13. exp Myocardial Infarction/
14. (myocardial$ adj3 infarction$).tw.
15. mi.tw.
16. (heart$ adj attack$).tw.
17. (heart$ adj3 infarction$).tw.
18. exp Angina, Unstable/
19. (unstable$ adj3 angina$).tw.
20. (preinfarction$ adj3 angina$).tw.
21. (myocardial$ adj3 preinfarction$).tw.
22. (unstable$ adj3 angina$ pectoris$).tw.
23. Myocardial Ischemia/
24. (myocardial$ adj3 ischemia$).tw.
25. (myocardial$ adj3 ischaemia$).tw.
26. (ischemic$ adj3 heart$ disease$).tw.
27. (ischaemic$ adj3 heart$ disease$).tw.
28. (heart$ adj3 muscle$ ischemia$).tw.

29. (heart$ adj3 muscle$ ischaemia$).tw.
30. or/10-29
31. exp Insulin/
32. (intensive$ adj3 insulin$ therap$).tw.
33. (intensive$ adj3 insulin$ infusion$).tw.
34. Glucose/
35. glucose$.tw.
36. (glucose$ adj3 therap$).tw.
37. (glucose$ adj3 infusion$).tw.
38. potassium.tw.
39. or/31-38
40. Randomized Controlled Trial.pt.
41. Controlled Clinical Trial.pt.
42. Clinical Trial.pt.
43. exp Clinical Trials as Topic/
44. Placebos/
45. Random Allocation/
46. Double-Blind Method/
47. Single-Blind Method/
48. Cross-Over Studies/
49. ((random$ or control$ or clinical$) adj2 (trial$ or stud$)).tw.
50. (random$ adj2 allocat$).tw.
51. placebo$.tw.
52. ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.
53. (crossover$ or (cross adj over$)).tw.
54. or/40-53
55. animals/ not humans/
56. 54 not 55
57. Meta-Analysis.pt.
58. Meta-Analysis as Topic/
59. Review.pt.
60. exp Review Literature as Topic/
61. (metaanaly$ or metanaly$ or (meta adj2 analy$)).tw.
62. (review$ or overview$).ti.

63. (systematic$ adj4 (review$ or overview$)).tw.
64. ((quantitative$ or qualitative$) adj4 (review$ or overview$)).tw.
65. ((studies or trial$) adj1 (review$ or overview$)).tw.
66. (integrat$ adj2 (research or review$ or literature)).tw.
67. (pool$ adj1 (analy$ or data)).tw.
68. (handsearch$ or (hand adj2 search$)).tw.
69. (manual$ adj2 search$).tw.
70. or/57-69
71. animals/ not humans/
72. 70 not 71
73. 54 or 72
74. 9 and 30 and 39 and 73
75. limit 74 to english language

At what stage should patients with hyperglycaemia and ACS without diagnosed diabetes be referred for subsequent investigations for possible diabetes?

Databases searched:

- Cochrane Central Register of Controlled Trials (Wiley)
- CINAHL (NHS Evidence)
- Cochrane Database of Systematic Reviews (Wiley)
- Database of Abstracts of Reviews of Effects (CRD)
- Embase (OVID)
- Health Technology Assessment database (CRD)
- Medline (OVID)
- Medline In-Process (OVID)

The searches were conducted on 06 October 2010.

The Medline search strategy is presented below. It was translated for use in all of the other databases.

Medline 1950 to September Week 3 2010

1. exp Hyperglycemia/

2. hyperglycemi$.tw.
3. hyperglycaemi$.tw.
4. (high$ adj3 plasma$ glucose$).tw.
5. (high$ adj3 blood$ glucose$).tw.
6. (impair$ adj3 glucose$ regulation$).tw.
7. (high$ adj3 blood$ sugar$).tw.
8. (impair$ adj3 blood$ sugar$ regulation$).tw.
9. or/1-8
10. Acute Coronary Syndrome/
11. (acute$ adj3 coronary$ syndrome$).tw.
12. acs.tw.
13. exp Myocardial Infarction/
14. (myocardial$ adj3 infarction$).tw.
15. mi.tw.
16. (heart$ adj attack$).tw.
17. (heart$ adj3 infarction$).tw.
18. exp Angina, Unstable/
19. (unstable$ adj3 angina$).tw.
20. (preinfarction$ adj3 angina$).tw.
21. (myocardial$ adj3 preinfarction$).tw.
22. (unstable$ adj3 angina$ pectoris$).tw.
23. Myocardial Ischemia/
24. (myocardial$ adj3 ischemia$).tw.
25. (myocardial$ adj3 ischaemia$).tw.
26. (ischemic$ adj3 heart$ disease$).tw.
27. (ischaemic$ adj3 heart$ disease$).tw.
28. (heart$ adj3 muscle$ ischemia$).tw.
29. (heart$ adj3 muscle$ ischaemia$).tw.
30. or/10-29
31. exp Diabetes Mellitus/
32. diabet$.tw.
33. or/31-32
34. Risk Factors/
35. (risk$ adj3 factor$).tw.

36. Blood Pressure/
37. (blood$ adj3 pressure$).tw.
38. Blood Glucose/
39. (blood$ adj3 glucose$).tw.
40. (plasma$ adj3 glucose$).tw.
41. (blood$ adj3 sugar$).tw.
42. exp Hematologic Tests/
43. (hematologic$ adj3 test$).tw.
44. (haematologic$ adj3 test$).tw.
45. (blood$ adj3 examination$).tw.
46 .Hemoglobin A, Glycosylated/
47. (glycosylated$ adj3 (hemoglobin$ or haemoglobin$)).tw.
48. hb a1c.tw.
49. hb a1.tw.
50. exp Obesity/
51. (obesity or obese).tw.
52. exp Cholesterol/
53. cholesterol$.tw.
54. or/34-53
55. 9 and 30 and 33 and 54
56. limit 55 to english language

What information should patients with peri ACS and hyperglycaemia (who are at high risk of developing diabetes) be provided while waiting for a referral for diagnostic investigations for diabetes?

Databases searched:

- Cochrane Central Register of Controlled Trials (Wiley)
- CINAHL (NHS Evidence)
- Cochrane Database of Systematic Reviews (Wiley)
- Database of Abstracts of Reviews of Effects (CRD)
- Embase (OVID)
- Health Technology Assessment database (CRD)
- Medline (OVID)

- Medline In-Process (OVID)

The searches were conducted on 2 November 2010.

The Medline search strategy is presented below. It was translated for use in all of the other databases. Where appropriate, search filters for patient information were appended to the search strategies to retrieve high quality papers.

Medline 1950 to October Week 3 2010

1. exp Hyperglycemia/
2. hyperglycemi$.tw.
3. hyperglycaemi$.tw.
4. (high$ adj3 plasma$ glucose$).tw.
5. (high$ adj3 blood$ glucose$).tw.
6. (impair$ adj3 glucose$ regulation$).tw.
7. (high$ adj3 blood$ sugar$).tw.
8. (impair$ adj3 blood$ sugar$ regulation$).tw.
9. or/1-8
10. Acute Coronary Syndrome/
11. (acute$ adj3 coronary$ syndrome$).tw.
12. acs.tw.
13. exp Myocardial Infarction/
14. (myocardial$ adj3 infarction$).tw.
15. mi.tw.
16. (heart$ adj attack$).tw.
17. (heart$ adj3 infarction$).tw.
18. exp Angina, Unstable/
19. (unstable$ adj3 angina$).tw.
20. (preinfarction$ adj3 angina$).tw.
21. (myocardial$ adj3 preinfarction$).tw.
22. (unstable$ adj3 angina$ pectoris$).tw.
23. Myocardial Ischemia/
24. (myocardial$ adj3 ischemia$).tw.

25. (myocardial$ adj3 ischaemia$).tw.
26. (ischemic$ adj3 heart$ disease$).tw.
27. (ischaemic$ adj3 heart$ disease$).tw.
28. (heart$ adj3 muscle$ ischemia$).tw.
29. (heart$ adj3 muscle$ ischaemia$).tw.
30. or/10-29
31. Qualitative Research/
32. Nursing Methodology Research/
33. exp Interviews as topic/
34. Questionnaires/
35. Narration/
36. Health Care Surveys/
37. (qualitative$ or interview$ or focus group$ or questionnaire$ or narrative$ or narration$ or survey$).tw.
38. (ethno$ or emic or etic or phenomenolog$ or grounded theory or constant compar$ or (thematic$ adj3 analys$) or theoretical sampl$ or purposive sampl$).tw.
39. (hermeneutic$ or heidegger$ or husserl$ or colaizzi$ or van kaam$ or van manen$ or giorgi$ or glaser$ or strauss$ or ricoeur$ or spiegelberg$ or merleau$).tw.
40. (metasynthes$ or meta-synthes$ or metasummar$ or meta-summar$ or metastud$ or meta-stud$).tw.
41. or/31-40
42. exp Patients/px
43. exp Parents/px
44. exp Family/px
45. Caregivers/px
46. Stress, Psychological/
47. (mental$ adj3 stress$).tw.
48. Adaptation, psychological/
49. (adaptive$ adj3 behaviour$).tw.
50. (adaptive$ adj3 behavior$).tw.
51. Emotions/
52. Anxiety/

53. Fear/
54. exp Consumer Satisfaction/
55. ((patient$ or parent$ or famil$ or carer$ or caregiver$ or care-giver$ or inpatient$ or in-patient$) adj2 (experience$ or belief$ or stress$ or emotion$ or anx$ or fear$ or concern$ or uncertain$ or unsure or thought$ or feeling$ or felt$ or view$ or opinion$ or perception$ or perspective$ or attitud$ or satisfact$ or know$ or understand$ or aware$)).tw.
56. or/42-55
57. Pamphlets/
58. Needs Assessment/
59. Information Centers/
60. Information Services/
61. Health Education/
62. Information Dissemination/
63. Counseling/
64. Social Support/
65. Self-Help Groups/
66. Self Care/
67. Patient Education as Topic/
68. Patient Education Handout/
69. Consumer Health Information/
70. Life Style/
71. patient* diar*.tw.
72. (educat$ or informat$ or communicat$ or pamphlet$ or handout$ or hand-out$ or hand out$ or booklet$ or leaflet$ or support$ or need$ or advice$ or advis$).ti.
73. (counsel$ or selfhelp$ or self-help$ or self help$ or selfcar$ or self-car$ or self car$).ti.
74. or/57-73
75. 41 or 56 or 74
76. 9 and 30 and 75
77. limit 76 to english language

**Economic search**

The following sources were searched to identify economic evaluations and quality of life data.

Databases searched:

- Health Economic Evaluations Database (Wiley)
- NHS Economic Evaluation Database (CRD)
- Embase(OVID)
- Medline (OVID)
- Medline In-Process (OVID)

The searches were conducted on 25 August 2010.

Medline1950 to August Week 2 2010

The Medline search strategy is presented below. It was translated for use in other databases except for Embase. Where appropriate, search filters for economic evaluations and quality of data were appended to the search strategies to retrieve high quality papers.

1. Acute Coronary Syndrome/
2. (acute$ adj3 coronary$ syndrome$).tw.
3. acs.tw.
4. exp Myocardial Infarction/
5. (myocardial$ adj3 infarction$).tw.
6. mi.tw.
7. (heart$ adj attack$).tw.
8. (heart$ adj3 infarction$).tw.
9. exp Angina, Unstable/
10. (unstable$ adj3 angina$).tw.
11. (preinfarction$ adj3 angina$).tw.
12. (myocardial$ adj3 preinfarction$).tw.
13. unstable$ adj3 angina$ pectoris$).tw.
14. Myocardial Ischemia/
15. (myocardial$ adj3 ischemia$).tw.

16. (myocardial$ adj3 ischaemia$).tw.
17. (ischemic$ adj3 heart$ disease$).tw.
18. (ischaemic$ adj3 heart$ disease$).tw.
19. (heart$ adj3 muscle$ ischemia$).tw.
20. (heart$ adj3 muscle$ ischaemia$).tw.
21. or/1-20
22. exp Insulin/
23. (intensive$ adj3 insulin$ therap$).tw.
24. (intensive$ adj3 insulin$ infusion$).tw.
25. Glucose/
26. glucose$.tw.
27. (glucose$ adj3 therap$).tw.
28. (glucose$ adj3 infusion$).tw.
29. potassium.tw.
30. or/22-29
31. 21 and 30
32. Economics/ use mesz
33. exp "Costs and Cost Analysis"/
34. Economics, Dental/
35. exp Economics, Hospital/
36. exp Economics, Medical/
37. Economics, Nursing/
38. Economics, Pharmaceutical/
39. Budgets/
40. exp Models, Economic/
41. Markov Chains/
42. Monte Carlo Method/
43. Decision Trees/
44. econom$.tw.
45. cba.tw.
46. cea.tw.
47. cua.tw.
48. markov$.tw.
49. (monte adj carlo).tw.

50. (decision adj2 (tree$ or analys$)).tw.
51. (cost or costs or costing$ or costly or costed).tw.
52. (price$ or pricing$).tw.
53. budget$.tw.
54. expenditure$.tw.
55. (value adj2 (money or monetary)).tw.
56. (pharmacoeconomic$ or (pharmaco adj economic$)).tw.
57. or/23-56
58. "Quality of Life"/ use mesz
59. quality of life.tw.
60. "Value of Life"/ use mesz
61 Quality-Adjusted Life Years/ use mesz
57. quality adjusted life.tw.
62. (qaly$ or qald$ or qale$ or qtime$).tw.
63. disability adjusted life.tw.
64. daly$.tw.
65. Health Status Indicators/ use mesz
66. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
67. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
68. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
69. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
70. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
71. (euroqol or euro qol or eq5d or eq 5d).tw.
72. (qol or hql or hqol or hrqol).tw.
73. (hye or hyes).tw.
74. health$ year$ equivalent$.tw.
75. utilit$.tw.
76. (hui or hui1 or hui2 or hui3).tw.

77. disutili$.tw.
78. rosser.tw.
79. quality of wellbeing.tw.
80. quality of well-being.tw.
81. qwb.tw.
82. willingness to pay.tw.
83. standard gamble$.tw.
84. time trade off.tw.
85. time tradeoff.tw.
86. tto.tw.
87. or/57-86
88. 57 or 87
89. 31 and 88
90. limit 89 to english language

## *Review questions and review protocols*

### Review questions

- 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?
- 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?
- What risk factors are associated with the development of diabetes in people with hyperglycaemia in ACS?
- What information should patients with ACS and hyperglycaemia (who are at high risk for developing diabetes) be provided before diagnostic investigations for diabetes?

### Review protocols

| **REVIEW QUESTION 1** | | |
|---|---|---|
| | **Details** | **Comments** |
| REVIEW QUESTION 1 | What is the optimal inpatient metabolic management of patients presenting | |

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|---|---|---|
| | with hyperglycaemia and acute coronary syndrome (ACS) who have diagnosed diabetes mellitus and hyperglycaemia? | |
| OBJECTIVES | To compare the effectiveness and safety of standard practice with intensive insulin therapy in the management of hyperglycaemia in ACS in patients who have been diagnosed with diabetes<br>To determine how and when glucose, potassium and/or insulin should be given to patients with hyperglycaemia and ACS<br>To investigate clinically acceptable targets of whole blood glucose level or plasma glucose level required to achieve normoglycemia<br>To determine when and how often whole blood or plasma glucose level should be measured in hospital | The wording of the objective was amended to include safety as adverse events such as hypoglycaemia were included as outcomes. |
| CRITERIA FOR CONSIDERING STUDIES | Inclusion:<br>Hyperglycaemia & ACS<br>Adults (> 18 years only)<br>Previous diagnosis of diabetes (type 1 or type2)<br>RCTs and MINAP<br>Treatment in first 48 hours only (acute phase)<br>Assessment of mortality and/or other primary/secondary outcome<br>Exclusion:<br>Other observational studies | |
| POPULATION | Adults with hyperglycaemia and ACS with diagnosed diabetes mellitus | |
| INTERVENTION | Intensive insulin therapy/infusion | |
| COMPARATORS | Standard practice/conventional treatment | |
| OUTCOMES | All cause mortality<br>Cardiovascular mortality<br>Cardiovascular events associated with hyperglycaemia such as non fatal reinfarction, heart failure and stroke<br>Measures of whole blood or plasma glucose levels<br>Health related quality of life<br>Adverse events associated with metabolic management of hyperglycaemia including | |

| | | |
|---|---|---|
| | hypoglycaemia and hypokalemia<br>Resource use and costs such as length of stay | |

| **REVIEW QUESTION 2** | | |
|---|---|---|
| | **Details** | **Comments** |
| REVIEW QUESTION 2 | What is the optimal inpatient metabolic management of patients presenting with hyperglycaemia and acute coronary syndrome (ACS) without a diagnosis of diabetes mellitus? | |
| OBJECTIVES | To compare the effectiveness and safety of standard practice with intensive insulin therapy in the management of hyperglycaemia in ACS in patients without a diagnosis of diabetes mellitus<br>To determine how and when glucose, potassium and/or insulin should be given to patients with hyperglycaemia and ACS<br>To investigate clinically acceptable targets of whole blood glucose level or plasma glucose level required to achieve normoglycemia<br>To determine when and how often whole blood or plasma glucose level should be measured in hospital | The wording of the objective was amended to include safety as adverse events such as hypoglycaemia were included as outcomes |
| CRITERIA FOR CONSIDERING STUDIES | Inclusion:<br>Hyperglycaemia & ACS<br>Adults (> 18 years only)<br>No previous diagnosis of diabetes<br>RCTs and MINAP<br>Treatment in first 48 hours only (acute phase)<br>Assessment of mortality and/or other primary/secondary outcome<br>Exclusion:<br>Other observational studies | |
| POPULATION | Adults with hyperglycaemia and ACS without diagnosed diabetes mellitus | |
| INTERVENTION | Intensive insulin therapy/infusion | |
| COMPARATORS | Standard practice/ conventional | |

| | | |
|---|---|---|
| | treatment | |
| OUTCOMES | All cause mortality Cardiovascular mortality<br>Cardiovascular events associated with hyperglycaemia such as non fatal reinfarction, heart failure and stroke<br>Measures of whole blood or plasma glucose levels<br>Health related quality of life<br>Adverse events associated with metabolic management of hyperglycaemia including hypoglycaemia and hypokalemia<br>Resource use and costs such as length of stay | |

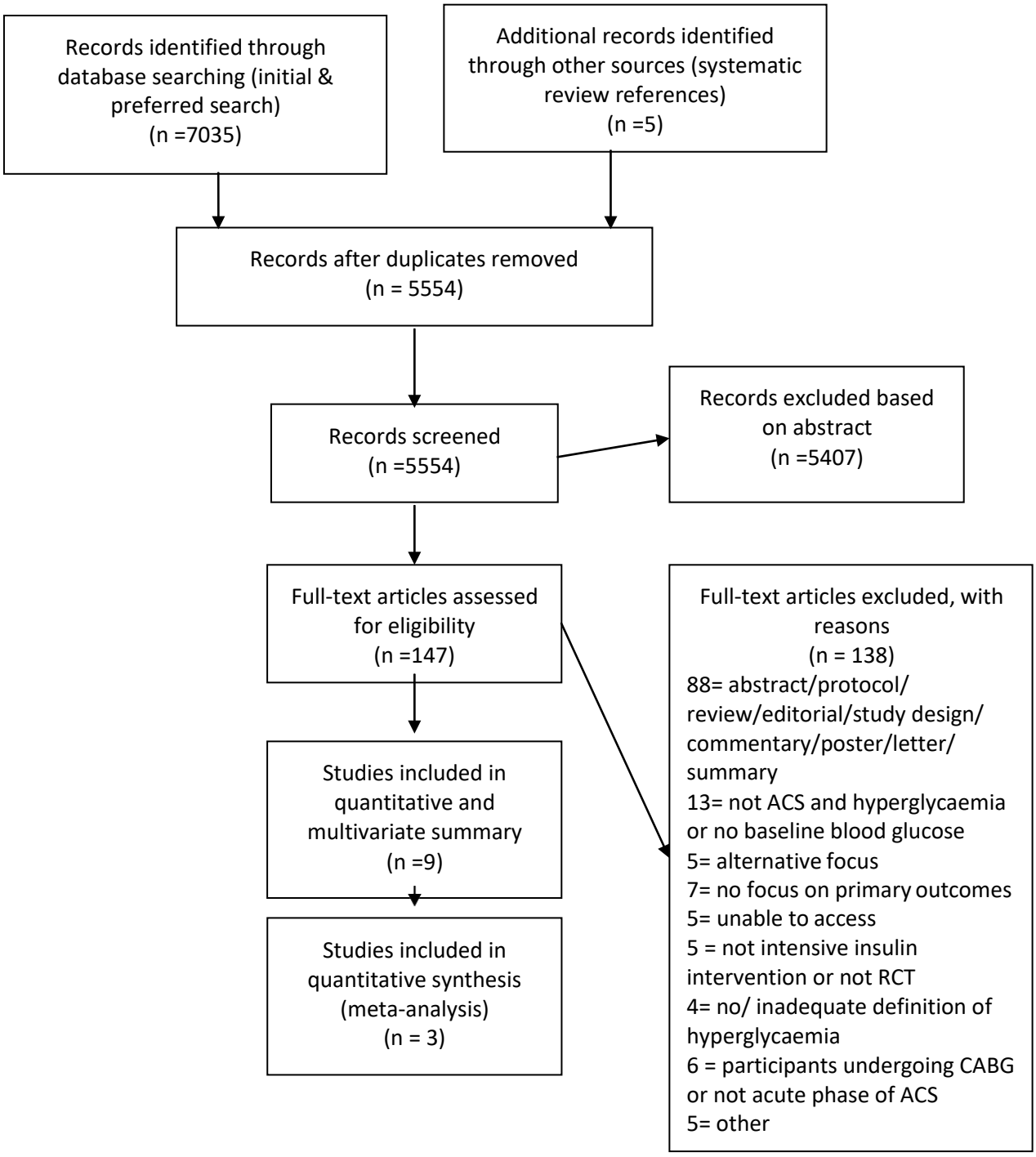
| **REVIEW QUESTION 3** | | |
|---|---|---|
| | **Details** | **Comments** |
| REVIEW QUESTION 3 | What risk factors are associated with diabetes in patients with hyperglycaemia and ACS who have not previously been diagnosed? | The GDG reworded this question to focus on the risk factors for progression to diabetes rather than the time at which patients should be referred. |
| OBJECTIVES | To investigate if the presence of additional risk factors which would prompt referral for investigations for diabetes | |
| CRITERIA FOR CONSIDERING STUDIES | Inclusion:<br>Adults (> 18 years only)<br>No previous diagnosis of diabetes<br>No restrictions on study design<br>Risk factors for diabetes (in ACS)<br>Signs and symptoms<br>Exclusion:<br>Already diagnosed with diabetes | |
| POPULATION | Adults with hyperglycaemia and ACS without diagnosed diabetes mellitus | |
| INTERVENTION | Intensive insulin therapy/infusion | |
| COMPARATORS | Standard practice/ conventional treatment | |
| OUTCOMES | Clinical signs and symptoms that lead to a referral for further investigation of possible diabetes | |

| | | |
|---|---|---|
| | Measures of whole blood or plasma glucose levels<br>Health related quality of life<br>Resource use and costs such as length of stay<br>Appropriate referral for subsequent investigations to confirm possible diabetes in patients without an existing diagnosis of diabetes. | |

| **REVIEW QUESTION 4** | | |
|---|---|---|
| | **Details** | **Comments** |
| REVIEW QUESTION 4 | What information should patients with peri ACS and hyperglycaemia (who are at high risk of developing diabetes) be provided while waiting for a referral for diagnostic investigations for diabetes? | |
| OBJECTIVES | To determine what information should be provided relating to the types of diagnostic investigations for diabetes<br>To determine what lifestyle advice should be provided | |
| CRITERIA FOR CONSIDERING STUDIES | Inclusion:<br>Adults (> 18 years only)<br>No previous diagnosis of diabetes<br>No restrictions on study design<br>Patient information/support<br>Exclusion:<br>Already diagnosed with diabetes | |
| POPULATION | Adults with hyperglycaemia and ACS without diagnosed diabetes mellitus | |
| INTERVENTION | Intensive insulin therapy/infusion | |
| COMPARATORS | Standard practice/ conventional treatment | |
| OUTCOMES | Patient and carer information and support needs<br>Health related quality of life<br>Appropriate referral for subsequent investigations to confirm possible diabetes in patients without an existing diagnosis of diabetes. | |

## *Flow diagram of excluded studies for hyperglycaemia review Question 1*

The flow diagram below shows an overview of the studies that were identified, included and excluded for review question 2, which focuses on the metabolic management of patients with ACS and hyperglycaemia who have diagnosed diabetes.



## *Excluded studies*

### List of excluded studies for review question 1 (diabetes)

Bianchi, C., Miccoli, R., Daniele, G., Penno, G., & Del, P.S. 2009. Is there evidence that oral hypoglycemic agents reduce cardiovascular morbidity/mortality? Yes. [Review] [53 refs]. Diabetes Care, 32, Suppl-8
Ref ID: 12A
EXC-NARRATIVE REVIEW

Mannucci, E., Monami, M., Lamanna, C., Gori, F., & Marchionni, N. 2009. Prevention of cardiovascular disease through glycemic control in type 2 diabetes: a meta-analysis of randomized clinical trials. Nutrition Metabolism & Cardiovascular Diseases, 19, (9) 604-612
Ref ID: 13A
EXC-REVIEW WITHOUT PERI ACS AND HYPERGLYCAEMIA AND FOCUS ON TYPE 2 DIABETES

Goyal, A., Mehta, S.R., Diaz, R., Gerstein, H.C., Afzal, R., Xavier, D., Liu, L., Pais, P., & Yusuf, S. 2009. Differential clinical outcomes associated with hypoglycemia and hyperglycemia in acute myocardial infarction. Circulation, 120, (24) 2429-2437
Ref ID: 15A
EXC-FOCUS ON PROGNOSTIC SIGNIFICANCE OF HYPERGLYCAEMIA ON ADMISSION

Avanzini, F., Marelli, G., Donzelli, W., Sorbara, L., Palazzo, E., Bellato, L., Colombo, E.L., Roncaglioni, M.C., Riva, E., De, M.M., & DDD study group 2009. Hyperglycemia during acute coronary syndrome: a nurse-managed insulin infusion protocol for stricter and safer control. European Journal of Cardiovascular Nursing, 8, (3) 182-189
Ref ID: 18A
EXC-PROTOCOL FOR INTENSIVE INSULIN AND NOT AN RCT

Monteiro, S., Monteiro, P., & Providencia, L.A. 2009. Optimization of blood glucose control in MI patients: state of the art and a proposed protocol for

intensive insulin therapy. [Review] [28 refs]. Revista Portuguesa de Cardiologia, 28, (1) 49-61
Ref ID: 22A
EXC-NARRATIVE REVEIW

Anantharaman, R., Heatley, M., & Weston, C.F. 2009. Hyperglycaemia in acute coronary syndromes: risk-marker or therapeutic target?. [Review] [65 refs]. Heart, 95, (9) 697-703
Ref ID: 26A
EXC-REVIEW

Gan, R.M., Wong, V., Cheung, N.W., & McLean, M. 2009. Effect of insulin infusion on electrocardiographic findings following acute myocardial infarction: importance of glycaemic control. Diabetic Medicine, 26, (2) 174-176
Ref ID: 30A
EXC-FOCUS ON ECG CHANGES AS AN OUTCOME

Goyal, A., Nerenberg, K., Gerstein, H.C., Umpierrez, G., & Wilson, P.W. 2008. Insulin therapy in acute coronary syndromes: an appraisal of completed and ongoing randomised trials with important clinical end points. [Review] [58 refs]. Diabetes & Vascular Disease Research, 5, (4) 276-284
Ref ID: 35A
EXC-REVIEW

Cheung, N.W. 2008. Glucose control during acute myocardial infarction. [Review] [20 refs]. Internal Medicine Journal, 38, (5) 345-348
Ref ID: 49A
EXC-NARRATIVE REVIEW

Braatvedt, G.D. 2008. Glucose control peri-myocardial infarction. [Review] [17 refs]. Internal Medicine Journal, 38, (5) 341-344
Ref ID: 50A
EXC-NARRATIVE REVIEW

Pinto, D.S., Kirtane, A.J., Pride, Y.B., Murphy, S.A., Sabatine, M.S., Cannon, C.P., Gibson, C.M., & CLARITY, T.I.M.I. 2008. Association of blood glucose

with angiographic and clinical outcomes among patients with ST-segment elevation myocardial infarction (from the CLARITY-TIMI-28 study). American Journal of Cardiology, 101, (3) 303-307
Ref ID: 53A
EXC-FOCUS ON USE OF CLOPIDOGREL

Diaz, R., Goyal, A., Mehta, S.R., Afzal, R., Xavier, D., Pais, P., Chrolavicius, S., Zhu, J., Kazmi, K., Liu, L., Budaj, A., Zubaid, M., Avezum, A., Ruda, M., & Yusuf, S. 2007. Glucose-insulin-potassium therapy in patients with ST-segment elevation myocardial infarction. JAMA, 298, (20) 2399-2405
Ref ID: 62A
EXC-COMBINED ANALYSIS OF CREATE ECLA AND OASIS-6. CREATE ECLA PAPER HAS BEEN EXCLUDED

Chaudhuri, A., Janicke, D., Wilson, M., Ghanim, H., Wilding, G.E., Aljada, A., & Dandona, P. 2007. Effect of modified glucose-insulin-potassium on free fatty acids, matrix metalloproteinase, and myoglobin in ST-elevation myocardial infarction. American Journal of Cardiology, 100, (11) 1614-1618
Ref ID: 63A
EXC-NOT PERI ACS AND HYPERGLYCAEMIA

Hafidh, S.A., Reuter, M.D., Chassels, L.J., Aradhyula, S., Bhutto, S.S., & Alpert, M.A. 2007. Effect of intravenous insulin therapy on clinical outcomes in critically ill patients. [Review] [56 refs]. American Journal of the Medical Sciences, 333, (6) 354-361
Ref ID: 70A
EXC-NARRATIVE REVIEW

Zarich, S.W. & Nesto, R.W. 2007. Implications and treatment of acute hyperglycemia in the setting of acute myocardial infarction. [Review] [23 refs]. Circulation, 115, (18) e436-e439
Ref ID: 73A
EXC-REVIEW

Cheung, N.W., Wong, V.W., & McLean, M. 2006. Insulin infusion therapy for myocardial infarction. [Review] [41 refs]. Expert Opinion on Pharmacotherapy,

7, (18) 2495-2503
Ref ID: 91A
EXC-REVIEW

Wade, A.O. & Cordingley, J.J. 2006. Glycaemic control in critically ill patients with cardiovascular disease. [Review] [51 refs]. Current Opinion in Critical Care, 12, (5) 437-443
Ref ID: 95A
EXC-REVIEW

Bhadriraju, S., Ray, K.K., DeFranco, A.C., Barber, K., Bhadriraju, P., Murphy, S.A., Morrow, D.A., McCabe, C.H., Gibson, C.M., Cannon, C.P., & Braunwald, E. 2006. Association between blood glucose and long-term mortality in patients with acute coronary syndromes in the OPUS-TIMI 16 trial. American Journal of Cardiology, 97, (11) 1573-1577
Ref ID: 100A
EXC-ORAL INTERVENTION-NOT INTENSIVE INSULIN THERAPY

Milicevic, Z., Raz, I., Strojek, K., Skrha, J., Tan, M.H., Wyatt, J.W., Beattie, S.D., Robbins, D.C., & Study, D. 2005. Hyperglycemia and its effect after acute myocardial infarction on cardiovascular outcomes in patients with Type 2 diabetes mellitus (HEART2D) Study design. Journal of Diabetes & its Complications, 19, (2) 80-87
Ref ID: 129A
EXC-NOT ACUTE EPISODE

Zarich, S.W. 2005. The role of intensive glycemic control in the management of patients who have acute myocardial infarction. [Review] [65 refs]. Cardiology Clinics, 23, (2) 109-117
Ref ID: 131A
EXC-NARRATIVE REVIEW

Imran, S.A., Malmberg, K., Cox, J.L., Ransom, T.P., & Ur, E. 2004. An overview of the role of insulin in the treatment of hyperglycemia during acute myocardial ischemia. [Review] [65 refs]. Canadian Journal of Cardiology, 20, (13) 1361-1365

Ref ID: 136A
EXC-NARRATIVE REVIEW

Pittas, A.G., Siegel, R.D., & Lau, J. 2004. Insulin therapy for critically ill hospitalized patients: a meta-analysis of randomized controlled trials. Archives of Internal Medicine, 164, (18) 2005-2011
Ref ID: 139A
EXC-REVIEW

Furnary, A.P., Gao, G., Grunkemeier, G.L., Wu, Y., Zerr, K.J., Bookin, S.O., Floten, H.S., & Starr, A. 2003. Continuous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting. Journal of Thoracic & Cardiovascular Surgery, 125, (5) 1007-1021
Ref ID: 164A
EXC-PARTICIPANTS UNDERGOING CABG

Dandona, P., Aljada, A., & Bandyopadhyay, A. 2003. The potential therapeutic role of insulin in acute myocardial infarction in patients admitted to intensive care and in those with unspecified hyperglycemia. [Review] [60 refs]. Diabetes Care, 26, (2) 516-519
Ref ID: 172A
EXC-COMMENTARY

McNulty, P.H. 2002. Glucose and insulin management in the post-MI setting. [Review] [51 refs]. Current Diabetes Reports, 2, (1) 37-44
Ref ID: 174A
EXC-NARRATIVE REVIEW

Davies, M.J. & Lawrence, I.G. 2002. DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction): theory and practice. [Review] [60 refs]. Diabetes, Obesity & Metabolism, 4, (5) 289-295
Ref ID: 177A
EXC-OVERVIEW OF DIGAMI STUDY

Walker, E.F. 1999. Management of diabetes and hyperglycaemia during myocardial infarction: review of the literature. [Review] [23 refs]. Intensive &

Critical Care Nursing, 15, (5) 259-265
Ref ID: 209A
EXC-NARRATIVE REVIEW

Rogers, W.J., Stanley, A.W., Jr., Breinig, J.B., Prather, J.W., McDaniel, H.G., Moraski, R.E., Mantle, J.A., Russell, R.O., Jr., & Rackley, C.E. 1976. Reduction of hospital mortality rate of acute myocardial infarction with glucose-insulin-potassium infusion. American Heart Journal, 92, (4) 441-454
Ref ID: 250A
EXC-NOT PERI ACS AND HYPERGLYCAEMIA AND NO BASELINE BLOOD GLUCOSE LEVELS

Hermanides, J., Engstrom, A.E., Wentholt, I.M., Sjauw, K.D., Hoekstra, J.B., Henriques, J.P., & DeVries, J.H. 2010. Sensor-augmented insulin pump therapy to treat hyperglycemia at the coronary care unit: a randomized clinical pilot trial. Diabetes Technology & Therapeutics, 12, (7) 537-542
Ref ID: 253A
EXC-NO FOCUS ON PRIMARY OUTCOMES

Langley, J. & Adams, G. 2007. Insulin-based regimens decrease mortality rates in critically ill patients: a systematic review. Diabetes/Metabolism Research and Reviews, 23, (3) 184-192
Ref ID: 275A
EXC-SYSTEMATIC REVIEW ON CRITICALLY ILL PATIENTS- NOT SPECIFIC TO ACS AND HYPERGLYCAEMIA

Devine, M.J., Chandrasekara, W.M., & Hardy, K.J. 2010. Management of hyperglycaemia in acute coronary syndrome. British Journal of Diabetes & Vascular Disease, 10, (2) 59-66
Ref ID: 287A
EXC-REVIEW

Rensing, K.L., Kastelein, J.J., & Twickler, M. 2009. Is insulin the preferred compound in lowering glucose levels in patients after a myocardial infarction?... Arch Intern Med. 2009 Mar 9;169(5):438-46. Archives of Internal Medicine, 169, (17) 1636-1639

Ref ID: 292A
EXC-COMMENT

Dandona, P., Chaudhuri, A., & Ghanim, H. 2009. Acute myocardial infarction, hyperglycemia, and insulin. Journal of the American College of Cardiology, 53, (16) 1437-1440
Ref ID: 297A
EXC-EDITORIAL

Kloner, R.A. & Nesto, R.W. 2008. Glucose-insulin-potassium for acute myocardial infarction: continuing controversy over cardioprotection. Circulation, 117, (19) 2523-2534
Ref ID: 305A
EXC-REVIEW

Smith, R.J. & McLean, M. 2008. Managing high blood glucose levels in coronary care. Internal Medicine Journal, 38, (5) 305-307
Ref ID: 306A
EXC-EDITORIAL

Opie, L.H. 2008. Metabolic management of acute myocardial infarction comes to the fore and extends beyond control of hyperglycemia. Circulation, 117, (17) 2172-2178
Ref ID: 308A
EXC-EDITORIAL

Black, S., Green, D., & Bryant, M. 2007. Role of tight glycaemic control for emergency department acute coronary syndrome patients... 6th International Conference for Emergency Nurses: Future Directions, Future ChallengesEL Beyond Tomorrow, 11-13 October 2007, Melbourne, Victoria, Australia. Australasian Emergency Nursing Journal, 10, (4) 193-194
Ref ID: 314A
EXC-CONFERENCE ABSTRACT

Jones, C. & Fisher, M. 2007. Intensive insulin treatment in coronary and intensive care. Practical Diabetes International, 24, (1) 42-48

Ref ID: 320A
EXC-NARRATIVE REVIEW

Mesotten, D. & Van den Berghe, G. 2003. Clinical potential of insulin therapy in critically ill patients. Drugs, 63, (7) 625-637
Ref ID: 333A
EXC-NARRATIVE REVIEW

Norhammar, A., Tenerz, Ã., Nilsson, G., Hamsten, A., Efendic, S., RydÃ©n, L., & Malmberg, K. 2002. Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. Lancet, 359, (9324) 2140-2145
Ref ID: 335A
EXC-NO INTERVENTION OF INTENSIVE INSULIN

Marfella, R., Di, F.C., Portoghese, M., Ferraraccio, F., Rizzo, M.R., Siniscalchi, M., Musacchio, E., D'Amico, M., Rossi, F., & Paolisso, G. 2009. Tight Glycemic Control Reduces Heart Inflammation and Remodeling During Acute Myocardial Infarction in Hyperglycemic Patients. Journal of the American College of Cardiology, 53, (16) 1425-1436
Ref ID: 357A
EXC-NO FOCUS ON PRIMARY OUTCOMES & COMPARING NORMOGLYCAEMIA WITH HYPERGLYCAEMIA

Inzucchi, S.E. 2008. Hyperglycaemia and its therapy during acute coronary syndromes. Diabetes and Vascular Disease Research, 5, (4) 259
Ref ID: 484A
EXC-EDITORIAL

Adams, G.G., Grainge, M., & Langley, J. 2008. Glucose-insulin-potassium (GIK) and tight-glycaemic-control (TGC) versus standard therapy insulin for critically ill patients. Cochrane Database of Systematic Reviews (1)
Ref ID: 518A
EXC-PROTOCOL

Chaudhuri, A., Nesto, R., & Dandona, P. 2008. Glucose-insulin-potassium therapy in patients with STEMI [4]. JAMA - Journal of the American Medical Association, 299, (20) 2386-2387
Ref ID: 520A
EXC-LETTER

Arora, R.R. & Katragadda, S. 2008. Glucose-insulin-potassium therapy in patients with STEMI [3]. JAMA - Journal of the American Medical Association, 299, (20) 2386
Ref ID: 521A
EXC-LETTER

Selker, H.P., Ingwall, J., & Rackley, C.E. 2008. Glucose-insulin-potassium therapy in patients with STEMI [1]. JAMA - Journal of the American Medical Association, 299, (20) 2385
Ref ID: 522A
EXC-LETTER

Loney-Hutchinson, L.M. & McFarlane, S.I. 2007. Glycemic control for hospitalized patients with diabetes: Strategies for effective management. Therapy, 4, (3) 217-220
Ref ID: 592A
EXC-NOT PROVIDED BY THE BRITISH LIBRARY

Gray, C.S., Hildreth, A.J., Sandercock, P.A., O'Connell, J.E., Johnston, D.E., Cartlidge, N.E., Bamford, J.M., James, O.F., & Alberti, K.G.M. 2007. Glucose-potassium-insulin infusions in the management of post-stroke hyperglycaemia: the UK Glucose Insulin in Stroke Trial (GIST-UK). Lancet Neurology, 6, (5) 397-406
Ref ID: 612A
EXC-REVIEW WITH FOCUS ON STROKE

Fitchett, D.H. 2007. Future strategies for improving outcomes in patients with diabetes and acute coronary syndromes. Future Cardiology, 3, (2) 115-121
Ref ID: 614A
EXC-EDITORIAL

Narain, V.S., Puri, A., & Ahuja, A. 2006. 10 Years of clinical trials in diabetic patient with coronary artery disease. Journal of Internal Medicine of India, 9, (1) 20-26
Ref ID: 620A
EXC-NARRATIVE REVIEW

Vanhorebeek, I., Ingels, C., & Van den Berghe, G. 2006. Intensive Insulin Therapy in High-Risk Cardiac Surgery Patients: Evidence from the Leuven Randomized Study. Seminars in Thoracic and Cardiovascular Surgery, 18, (4) 309-316
Ref ID: 632A
EXC-NARRATIVE REVIEW

Hirsch, I.B. 2006. Inpatient diabetes: Review of data from the cardiac care unit. Endocrine Practice, 12, (SUPPL. 3) 27-34
Ref ID: 635A
EXC-NARRATIVE REVIEW

Hasin, T., Eldor, R., & Hammerman, H. 2006. Intensive insulin therapy in the intensive cardiac care unit. Acute Cardiac Care, 8, (4) 181-185
Ref ID: 637A
EXC-NARRATIVE REVIEW

Henderson, W.R., Chittock, D.R., Dhingra, V.K., & Ronco, J.J. 2006. Hyperglycemia in acutely ill emergency patients - Cause or effect? Canadian Journal of Emergency Medicine, 8, (5) 339-343
Ref ID: 654A
EXC-REVIEW

Soran, H., Barzangy, B., & Younis, N. 2006. The benefits of insulin therapy following acute myocardial infarction revisited. QJM, 99, (9) 635-637
Ref ID: 656A
EXC-COMMENTARY

Pittas, A.G., Siegel, R.D., & Lau, J. 2006. Insulin therapy and in-hospital mortality in critically ill patients: Systematic review and meta-analysis of

randomized controlled trials. Journal of Parenteral and Enteral Nutrition, 30, (2) 164-172
Ref ID: 665A
EXC-REVIEW

Furnary, A.P. & Braithwaite, S.S. 2006. Effects of Outcome on In-Hospital Transition from Intravenous Insulin Infusion to Subcutaneous Therapy. American Journal of Cardiology, 98, (4) 557-564
Ref ID: 671A
EXC-NARRATIVE REVIEW

Devos, P., Chiolero, R., Van den Berghe, G., & Preiser, J.-C. 2006. Glucose, insulin and myocardial ischaemia. Current Opinion in Clinical Nutrition and Metabolic Care, 9, (2) 131-139
Ref ID: 673A
EXC-REVIEW

Vogelzang, M., Svilaas, T., van der Horst, I.C.C., Nijsten, M.W.N., & Zijlstra, F. 2006. Refractory hyperglycaemia induced by glucose-insulin-potassium infusion in acute myocardial infarction. Netherlands Heart Journal, 14, (2) 46-48
Ref ID: 696A
EXC-FOCUS ON ASSOCIATION BETWEEN HIGH DOSE INSULIN INFUSION AND REFRACTORY HYPERGLYCAEMIA

Rasoul, S., Svilaas, T., Ottervanger, J.-P., Timmer, J.R., Van't Hof, A.W.J., & Zijlstra, F. 2006. A quantitative analysis of the effect of glucose-insulin-potassium in acute myocardial infarction. Netherlands Heart Journal, 14, (1) 19-23
Ref ID: 697A
EXC-REVIEW

van der Horst, I.C.C. & Zijlstra, F. 2005. Role for insulin in acute myocardial infarction: Ruled out or hard to prove? [1]. European Heart Journal, 26, (23) 2600

Ref ID: 714A
EXC-LETTER

van der Horst, I.C.C. & Zijlstra, F. 2005. GIK in acute myocardial infarction: Lessons from CREATE-ECLA, GIPS II and DIGAMI 2. Netherlands Heart Journal, 13, (7-8) 251-253
Ref ID: 724A
EXC-EDITORIAL

Holt, R.I.G. 2005. DIGAMI-2 - The optimal management of hyperglycaemia remains controversial. Diabetes, Obesity and Metabolism, 7, (1) 110-116
Ref ID: 754A
EXC-COMMENTARY

Vaage, J. 2004. Glucose-insulin-potassium in cardiac surgery: A meta-analysis. Invited commentary. Annals of Thoracic Surgery, 78, (5) 1658
Ref ID: 778A

EXC- COMMENTARY

Bretzel, R.G. 2004. Intensive insulin regimens: Evidence for benefit. International Journal of Obesity, 28, (SUPPL. 2) S8-S13
Ref ID: 782A
EXC-REVIEW

Lazar, H.L. 2003. Tight glycemic control essential in diabetics undergoing CABG surgery. Cardiology Review, 20, (2) 22
Ref ID: 852A

EXC-NOT PROVIDED BY THE BRITISH LIBRARY

Davey, G. & McKeigue, P. 1996. Insulin infusion in diabetic patients with acute myocardial infarction. Effective in diabetes, but patients with glucose intolerance may also benefit. British Medical Journal, 313, (7058) 639-640
Ref ID: 927A
EXC-EDITORIAL

Hemmingsen, B., Lund, S.S., Gluud, C., Vaag, A., Almdal, T., & Wetterslev, J. 2009. Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus. Cochrane Database of Systematic Reviews (4)
Ref ID: 958A
EXC-PROTOCOL

Benito, B., Conget, I., Bosch, X., Heras, M., Ordóñez, J., Sionis, A., Díaz, G., & Esmatjes, E. 2008. [Intensive insulin therapy in non-diabetic patients with myocardial infarction and hyperglycemia. INSUCOR study]. Medicina clínica, 130, (16) 601-605
Ref ID: 983A
EXC-NON-ENGLISH

Misso, M.L., Egberts, K.J., Page, M., O'Connor, D., & Shaw, J. 2010. Continuous subcutaneous insulin infusion (CSII) versus multiple insulin injections for type 1 diabetes mellitus. Cochrane Database of Systematic Reviews (1)
Ref ID: 1

EXC-NOT PERI ACS AND HYPERGLYCAEMIA

Lankisch, M., Füth, R., Gülker, H., Lapp, H., Bufe, A., Haastert, B., Martin, S., & Rathmann, W. 2008. Screening for undiagnosed diabetes in patients with acute myocardial infarction. Clinical research in cardiology : official journal of the German Cardiac Society, 97, (10) 753-759
Ref ID: 81
EXC-NOT AN RCT

Bucciarelli-Ducci, C., Bianchi, M., De, L.L., Battagliese, A., Di, R.C., Proietti, P., Vizza, C.D., & Fedele, F. 2006. Effects of glucose-insulin-potassium infusion on myocardial perfusion and left ventricular remodeling in patients treated with primary angioplasty for ST-elevation acute myocardial infarction. The American journal of cardiology, 98, (10) 1349-1353
Ref ID: 135

EXC-NO FOCUS ON PRIMARY OUTCOMES AND NO RECORD OF BLOOD GLUCOSE STATES

Krljanac, G., Vasiljevi&#263, Z, Radovanovi&#263, M, Stankovi&#263, G, Mili&#263, N, Stefanovi&#263, B, Kosti&#263, J, Mitrovi&#263, P, Radovanovi&#263, N, Dragovi&#263, M, Marinkovi&#263, J, Karadzi&#263, & A 2005. Effects of glucose-insulin-potassium infusion on ST-elevation myocardial infarction in patients treated with thrombolytic therapy. The American journal of cardiology, 96, (8) 1053-1058
Ref ID: 174
EXC-NOT PERI ACS AND HYPERGLYCAEMIA

Stefanidis, A., Melidonis, A., Tournis, S., Zairis, M., Handanis, S., Beldekos, D., Argyrakis, S., Asimacopoulos, P., & Foussas, S. 2003. Effect of intravenous insulin administration on left ventricular performance during non-ST-elevation acute coronary events in patients with diabetes mellitus. The American journal of cardiology, 91, (10) 1237-1240
Ref ID: 238
EXC-NO FOCUS ON PRIMARY OUTCOMES AND CONTROL GROUP ALSO RECEIVED INSULIN IF BLOOD GLUCOSE ABOVE SPECIFIC THRESHOLD

Rymarz, E., Mosiewicz, J., & Hanzlik, J. 2003. The influence of polarizing GIK mixture on the indicators of myocardial necrosis. Annales Universitatis Mariae Curie-Skłodowska.Sectio D: Medicina, 58, (1) 5-10
Ref ID: 253

EXC-NOT PROVIDED BY THE BRITISH LIBRARY

Melidonis, A., Stefanidis, A., Tournis, S., Manoussakis, S., Handanis, S., Zairis, M., Dadiotis, L., & Foussas, S. 2000. The role of strict metabolic control by insulin infusion on fibrinolytic profile during an acute coronary event in diabetic patients. Clinical cardiology, 23, (3) 160-164
Ref ID: 320
EXC-FIBRINOLYTIC FUBCTION IS NOT A PRIMARY OUTCOME

Díaz, R., Paolasso, E.A., Piegas, L.S., Tajer, C.D., Moreno, M.G., Corvalán, R., Isea, J.E., & Romero, G. 1998. Metabolic modulation of acute myocardial infarction. The ECLA (Estudios Cardiológicos Latinoamérica) Collaborative Group. Circulation, 98, (21) 2227-2234
Ref ID: 349
EXC-NO DEFINITION OF HYPERGLYCAEMIA

Yang, Z.H., Yang, K.H., Ma, B., & Yin, S.F. 2008. Effect of glucose-insulin-potassium on heart function of patients with acute myocardial infarction: a systematic review. Chinese Journal of Evidence-Based Medicine, 8, (2) 97-101
Ref ID: 556
EXC-NON-ENGLISH

Mamas, M.A., Neyses, L., & Fath-Ordoubadi, F. 2010. A meta-analysis of glucose-insulin-potassium therapy for treatment of acute myocardial infarction. Experimental & Clinical Cardiology, 15, (2) e2--e24
Ref ID: 574
EXC-REVIEW WITH NO FOCUS ON HYPERGLYCAEMIA

Opie, L.H. 2008. Glucose-insulin-potassium therapy in patients with STEMI... JAMA. 2007 Nov 28;298(20):2399-405. JAMA: Journal of the American Medical Association, 299, (20) 2385-2389
Ref ID: 734
EXC-LETTER

Arora, R.R. & Katragadda, S. 2008. Glucose-insulin-potassium therapy in patients with STEMI... JAMA. 2005 Jan 26;293(4):437-46; JAMA. 2007 Nov 28;298(20):2399-405. JAMA: Journal of the American Medical Association, 299, (20) 2386-2389
Ref ID: 735

EXC-LETTER

Chaudhuri, A., Nesto, R., & Dandona, P. 2008. Glucose-insulin-potassium therapy in patients with STEMI... JAMA. 2007 Nov 28;298(20):2399-405. JAMA: Journal of the American Medical Association, 299, (20) 2386-2389
Ref ID: 736
EXC-LETTER

Chaudhuri, A., Miller, M., Nesto, R., Rosenberg, N., & Dandona, P. 2007. Targeting glucose in acute myocardial infarction: has glucose, insulin, and potassium infusion missed the target? Diabetes care, 30, (12) 3026-3029
Ref ID: 778
EXC-NOT AN RCT

Murphy, S.A. 2006. OASIS-6 -- Glucose-Insulin-Potassium (OASIS-6 -- GIK). ACC Cardiosource Review Journal 38-39
Ref ID: 825
EXC-CONFERENCE POSTER

Timmer, J.R., Svilaas, T., Ottervanger, J.P., Henriques, J.P., Dambrink, J.H., van den Broek, S.A., van der Horst, I.C., & Zijlstra, F. 2006. Glucose-insulin-potassium infusion in patients with acute myocardial infarction without signs of heart failure: the Glucose-Insulin-Potassium Study (GIPS)-II. Journal of the American College of Cardiology, 47, (8) 1730-1732
Ref ID: 878
EXC-LETTER TO EDITOR

Yusuf, S. 2005. Intensive insulin-glucose infusion regimens with long-term or standard glucose control did not differ for reducing mortality in type 2 diabetes mellitus and MI. ACP Journal Club, 143, (2) 43-44
Ref ID: 919
EXC-SUMMARY OF DIGAMI 2

Mukherjee, D. 2005. [Commentary on] Intensive metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. ACC Current Journal Review, 14, (7) 6-7

Ref ID: 927
EXC-COMMENT

Berger, P.B. 2005. A glucose-insulin-potassium infusion did not reduce, mortality, cardiac arrest, or cardiogenic shock after acute MI. ACP Journal Club, 143, (1) 4-6
Ref ID: 929
EXC-COMMENTARY AND NOT PERI ACS AND HYPERGLYCAEMIA

Apstein, C.S., Cobb, L.A., Killip, T., Lambrew, C.T., MacLeod, B.A., Rackley, C.E., Selker, H.P., Zalenski, R.J., Dey, J., Blonde, L., Burshell, A., Bolton, P., Richard, A., Mehta, S.R., Yusuf, S., Diaz, R., & Paolasso, E. 2005. Glucose-insulin-potassium infusion and mortality in the CREATE-ECLA trial... Mehta SR, Yusuf S, Diaz R et al. Effect of glucose-insulin-potassium infusion on mortality in patients with acute ST-segment elevation myocardial infarction. JAMA. 2005;293:437-446. JAMA: Journal of the American Medical Association, 293, (21) 2596-2599
Ref ID: 937
EXC-LETTER

Rubenfire, M. 2005. [Commentary on] Effect of glucose-insulin-potassium infusion on mortality in patients with acute ST-segment elevation myocardial infarction. The CREATE-ECLA randomized controlled trial. ACC Current Journal Review, 14, (4) 9-10
Ref ID: 941
EXC-COMMENTARY

2005. Effect of glucose-insulin-potassium infusion on mortality in patients with acute ST-segment elevation myocardial infarction: the CREATE-ECLA randomized controlled trial. JAMA: Journal of the American Medical Association, 293, (4) 437-447
Ref ID: 951
EXC-NO PRECISE DEFINITION OF HYPERGLYCAEMIA AND BLOOD GLUCOSE LEVELS

Mak, K.H. & Topol, E.J. 2000. Emerging concepts in the management of acute myocardial infarction in patients with diabetes mellitus. Journal of the American College of Cardiology, 35, (3) 563-569
Ref ID: 1082
EXC-FOCUS ON FIBRINOLYSIS

1999. AMI treatment rejected in '60s draws new attention: GIK cuts death rate in half. Cost Management in Cardiac Care, 4, (2) 21-23
Ref ID: 1104
EXC-COMMENT

Marso, S.P., Kennedy, K.F., House, J.A., & McGuire, D.K. 2010. The effect of intensive glucose control on all-cause and cardiovascular mortality, myocardial infarction and stroke in persons with type 2 diabetes mellitus: a systematic review and meta-analysis. [Review] [30 refs]. Diabetes & Vascular Disease Research, 7, (2) 119-130
Ref ID: 1189
EXC-REVIEW

Conget, I. & Gimenez, M. 2009. Glucose control and cardiovascular disease: is it important? No. [Review] [25 refs]. Diabetes care, 32, Suppl-6
Ref ID: 1223
EXC-BRITISH LIBRARY NOT ABLE TO SUPPLY

Ray, K.K., Seshasai, S.R., Wijesuriya, S., Sivakumaran, R., Nethercott, S., Preiss, D., Erqou, S., & Sattar, N. 2009. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. Lancet, 373, (9677) 1765-1772
Ref ID: 1262
EXC-REVIEW-NO FOCUS ON THE ACUTE PHASE OF ACS

Malmberg, K. & Ryden, L. 2006. Effect of insulin-glucose infusion on mortality following acute myocardial infarction in patients with diabetes: the diabetes and insulin-glucose infusion in acute myocardial infarction studies. [Review] [15 refs]. Seminars in Thoracic & Cardiovascular Surgery, 18, (4) 326-329

Ref ID: 1464
EXC-NARRATIVE REVIEW

Schipke, J.D., Friebe, R., & Gams, E. 2006. Forty years of glucose-insulin-potassium (GIK) in cardiac surgery: a review of randomized, controlled trials. [Review] [70 refs]. European Journal of Cardio-Thoracic Surgery, 29, (4) 479-485
Ref ID: 1531
EXC-REVIEW OF CARDIAC SURGERY

Turel, B., Gemici, K., Baran, I., Yesilbursa, D., Gullulu, S., Aydinlar, A., Serdar, A., Kazazoglu, A.R., Kumbay, E., & Cordan, J. 2005. Effects of glucose-insulin-potassium solution added to reperfusion treatment in acute myocardial infarction. Anadolu Kardiyoloji Dergisi, 5, (2) 90-94
Ref ID: 1642
EXC-NOT PERI ACS AND HYPERGLYCAEMIA AND NO BASELINE RECORD OF BLOOD GLUCOSE

Timmer, J.R., van der Horst, I.C., Ottervanger, J.P., De, L.G., van 't Hof, A.W., Bilo, H.J., & Zijlstra, F. 2004. Glucose-insulin-potassium infusion as adjunctive therapy in myocardial infarction: current evidence and potential mechanisms. Italian Heart Journal: Official Journal of the Italian Federation of Cardiology, 5, (10) 727-731
Ref ID: 1682
EXC-REVIEW

Apstein, C.S. 2003. The benefits of glucose-insulin-potassium for acute myocardial infarction (and some concerns). [Review] [30 refs]. Journal of the American College of Cardiology, 42, (5) 792-795
Ref ID: 1796
EXC-EDITORIAL COMMENT

Janiger, J.L. & Cheng, J.W. 2002. Glucose-insulin-potassium solution for acute myocardial infarction. [Review] [14 refs]. Annals of Pharmacotherapy, 36, (6) 1080-1084

Ref ID: 1887
EXC-NARRATIVE REVIEW

Ceremuzynski, L., Budaj, A., Czepiel, A., Burzykowski, T., Achremczyk, P., Smielak-Korombel, W., Maciejewicz, J., Dziubinska, J., Nartowicz, E., Kawka-Urbanek, T., Piotrowski, W., Hanzlik, J., Cieslinski, A., Kawecka-Jaszcz, K., Gessek, J., & Wrabec, K. 1999. Low-dose glucose-insulin-potassium is ineffective in acute myocardial infarction: results of a randomized multicenter Pol-GIK trial. Cardiovascular Drugs & Therapy, 13, (3) 191-200
Ref ID: 2044
EXC-NO PERI ACS AND HYPERGLYCAEMIA

Apstein, C.S. & Opie, L.H. 1999. Glucose-insulin-potassium (GIK) for acute myocardial infarction: a negative study with a positive value. [Review] [38 refs]. Cardiovascular Drugs & Therapy, 13, (3) 185-189
Ref ID: 2045
EXC-EDITORIAL

Fath-Ordoubadi, F. & Beatt, K.J. 1999. Glucose-insulin-potassium in acute myocardial infarction. Lancet, 353, (9168) 1968
Ref ID: 2050
EXC-CORRESPONDENCE

Fisher, M. 1999. Diabetes and myocardial infarction. [Review] [56 refs]. Best Practice & Research Clinical Endocrinology & Metabolism, 13, (2) 331-343
Ref ID: 2078
EXC-NARRATIVE REVIEW

Apstein, C.S. 1998. Glucose-insulin-potassium for acute myocardial infarction: remarkable results from a new prospective, randomized trial. [Review] [27 refs]. Circulation, 98, (21) 2223-2226
Ref ID: 2102
EXC-EDITIORIAL

Williams, R. 1997. Intensive insulin treatment after acute myocardial infarction in diabetes mellitus. Evidence exists from study of non-insulin dependent

diabetes in Japan. BMJ, 315, (7107) 544
Ref ID: 2168
EXC-EDITORIAL

Surawicz, B. 1968. Evaluation of treatment of acute myocardial infarction with potassium, glucose and insulin. [Review] [110 refs]. Progress in Cardiovascular Diseases, 10, (6) 545-560
Ref ID: 2692
EXC-NARRATIVE REVIEW

Rogers, W.J., McDaniel, H.G., Mantle, J.A., & Rackley, C.E. 1982. Glucose-insulin-potassium infusion in acute myocardial infarction - results of a prospective randomized study. Clinical Research, 30, (2) 216A
Ref ID: 2877
EXC-ABSTRACT ONLY

Stanley, J., Prather, J.W., & Snow, R.M. 1979. Glucose-insulin-potassium, acute myocardial infarction and patient mortality: Results from an ongoing prospective randomized study. Clinical Research, 27, (5) 734A
Ref ID: 2921
EXC-ABSTRACT ONLY

Puskarich, M., Jones, A., Kline, J., Runyon, M., & Trzeciak, S. 2009. Critical Care, Conference: 29th International Symposium on Intensive Care and Emergency Medicine Brussels Belgium. Conference Start: 20090324 Conference End: 20090327. Conference: 29th International Symposium on Intensive Care and Emergency Medicine Brussels Belgium. Conference Start: 20090324 Conference End: 20090327. Conference Publication: (var.pagings) S54
Ref ID: 3462
EXC-BRITISH LIBRARY CANNOT PROVIDE A COPY

Cefalu, W.T. & Watson, K. 2008. Intensive glycemic control and cardiovascular disease observations from the ACCORD study: Now what can a clinician possibly think? Diabetes, 57, (5) 1163-1165

Ref ID: 3525
EXC-EDITORIAL

Goyal, A., Nerenberg, K., Gerstein, H.C., Umpierrez, G., & Wilson, P.W.F. 2008. Insulin therapy in acute coronary syndromes: An appraisal of completed and ongoing randomised trials with important clinical end points. Diabetes and Vascular Disease Research, 5, (4) 276-284
Ref ID: 3585
EXC-REVIEW

Goyal, A., Diaz, R., & Mehta, S.R. 2008. Glucose-insulin-potassium therapy in patients with STEMI: Reply. JAMA - Journal of the American Medical Association, 299, (20) 2387-2388
Ref ID: 3696
EXC-LETTER

Opie, L.H. 2008. Glucose-insulin-potassium therapy in patients with STEMI [2]. JAMA - Journal of the American Medical Association, 299, (20) 2385-2386
Ref ID: 3697
EXC-LETTER

Ranasinghe, A.M., Quinn, D.W., Pagano, D., Edwards, N., Faroqui, M., Graham, T.R., Keogh, B.E., Mascaro, J., Riddington, D.W., Rooney, S.J., Townend, J.N., Wilson, I.C., & Bonser, R.S. 2006. Glucose-insulin-potassium and tri-iodothyronine individually improve hemodynamic performance and are associated with reduced troponin I release after on-pump coronary artery bypass grafting. Circulation, 114, (SUPPL. 1) I245-I250
Ref ID: 4253
EXC-PARTCIPANTS UNDERGOING CABG

Yazici, M., Demircan, S., Durna, K., Yasar, E., Acar, Z., & Sahin, M. 2005. Effect of glucose-insulin-potassium infusion on myocardial damage due to percutaneous coronary revascularization. American Journal of Cardiology, 96, (11) 1517-1520
Ref ID: 4456
EXC-NO FOCUS ON PRIMARY OUTCOMES

2005. Effect of glucose-insulin-potassium infusion on mortality in patients with acute ST-segment elevation myocardial infarction: Comments. Indian Heart Journal, 57, (2) 187
Ref ID: 4535
EXC-COMMENT

van der Horst, I.C.C., De, L.G., Ottervanger, J.P., de, B.M.J., Hoorntje, J.C.A., Suryapranata, H., Dambrink, J.-H., Gosselink, A.T.M., Zijlstra, F., & Van 't Hof, A.W.J. 2005. ST-segment elevation resolution and outcome in patients treated with primary angioplasty and glucose-insulin-potassium infusion. American heart journal, 149, (6) 1135
Ref ID: 4555
EXC-NOT PERI ACS AND HYPERGLYCAEMIA AND NO EVALUATION OF BASELINE BLOOD GLUCOSE

van der Horst, I.C.C., Timmer, J.R., Ottervanger, J.P., Bilo, H.J.G., Gans, R.O.B., de, B.M.J., & Zijlstra, F. 2005. Glucose-insulin-potassium and reperfusion in acute myocardial infarction: Rationale and design of the Glucose-Insulin-Potassium Study-2 (GIPS-2). American heart journal, 149, (4) 585-591
Ref ID: 4601
EXC-NO MENTION OF BASELINE BLOOD GLUCOSE

Zhang, L., Li, Y.H., Zhang, H.Y., Chen, M.L., Gao, M.-M., Hu, A.H., Yang, H.S., & Liu, L.S. 2005. High-dose glucose-insulin-potassium treatment reduces myocardial apoptosis in patients with acute myocardial infarction. European journal of clinical investigation, 35, (3) 164-170
Ref ID: 4630
EXC-NOT PERI ACS AND HYPERGLYCAEMIA AND NO EVALUATION OF BASELINE BLOOD GLUCOSE

Yusuf, S., Mehta, S.R., Diaz, R., Paolasso, E., Pais, P., Xavier, D., Xie, C., Ahmed, R.J., Khazmi, K., Zhu, J., & Liu, L. 2004. Challenges in the conduct of large simple trials of important generic questions in resource-poor settings: The CREATE and ECLA trial program evaluating GIK (glucose, insulin and

potassium) and low-molecular-weight heparin in acute myocardial infarction. American heart journal, 148, (6) 1068-1078
Ref ID: 4705
EXC-RELATES TO STUDY DESIGN

Kastrati, A. & Bellandi, F. 2004. Trial finds routine intravenous glucose-insulin-potassium does not improve myocardial salvage in people with acute myocardial infarction. Evidence-based Cardiovascular Medicine, 8, (4) 339-342
Ref ID: 4707
EXC-NOT PERI ACS AND HYPERGLYCAEMIA

Lazar, H.L., Chipkin, S.R., Fitzgerald, C.A., Bao, Y., Cabral, H., & Apstein, C.S. 2004. Tight Glycemic Control in Diabetic Coronary Artery Bypass Graft Patients Improves Perioperative Outcomes and Decreases Recurrent Ischemic Events. Circulation, 109, (12) 1497-1502
Ref ID: 4850
EXC-PARTICIPANTS UNDERGOING CABG

Castro, P.F., Larrain, G., Baeza, R., Corbalan, R., Nazzal, C., Greig, D.P., Miranda, F.P., Perez, O., Acevedo, M., Marchant, E., Olea, E., & Gonzalez, R. 2003. Effects of glucose-insulin-potassium solution on myocardial salvage and left ventricular function after primary angioplasty. Critical care medicine, 31, (8) 2152-2155
Ref ID: 5004
EXC-NOT PERI ACS AND HYPERGLYCAEMIA

Stefanidis, A., Melidonis, A., Tournis, S., Zairis, M., Handanis, S., Olympios, C., Asimacopoulos, P., & Foussas, S. 2002. Intensive insulin treatment reduces transient ischaemic episodes during acute coronary events in diabetic patients. Acta Cardiologica, 57, (5) 357-364
Ref ID: 5150
EXC-HYPERGLYCAEMIC POPULATION NOT WELL DEFINED AND DOES NOT DEFINE BLOOD GLUCOSE ON RECRUITMENT

Diaz-Araya, G., Nettle, D., Castro, P., Miranda, F., Greig, D., Campos, X., Chiong, M., Nazzal, C., Corbalan, R., & Lavandero, S. 2002. Oxidative stress after reperfusion with primary coronary angioplasty: Lack of effect of glucose-insulin-potassium infusion. Critical care medicine, 30, (2) 417-421
Ref ID: 5220
EXC-NOT PERI ACS AND HYPERGLYCAEMIA AND OXIDATIVE STRESS NOT A PRIMARY OUTCOME

Fath-Ordoubadi, F., Markides, V., & Beatt, K.J. 1998. Meta-analysis of glucose-insulin-potassium therapy for myocardial infarction. Cardiology Review, 15, (4) 41-44
Ref ID: 5511
EXC-REVIEW ARTICLE NOT FOCUSING ON PERI ACS AND HYPERGLYCAEMIA

Fath-Ordoubadi, F. & Beatt, K.J. 1997. Glucose-insulin-potassium therapy for treatment of acute myocardial infarction: An overview of randomized placebo-controlled trials. Circulation, 96, (4) 1152-1156
Ref ID: 5571
EXC-REVIEW

Mellbin, L.G., Malmberg, K., Norhammar, A., Wedel, H., & Ryden, L. 2008. The impact of glucose lowering treatment on long-term prognosis in patients with type 2 diabetes and myocardial infarction: A report from the DIGAMI 2 trial. European heart journal, 29, (2) 166-176
Ref ID: 5618
EXC-FOCUS ON TREATMENT FOLLOWING DISCHARGE (NOT ACUTE PHASE)

Rasoul, S., Ottervanger, J.P., Timmer, J.R., Svilaas, T., Henriques, J.P.S., Dambrink, J.-H., van der Horst, I.C.C., & Zijlstra, F. 2007. One year outcomes after glucose-insulin-potassium in ST elevation myocardial infarction. The Glucose-insulin-potassium study II. International journal of cardiology, 122, (1) 52-55

Ref ID: 5703
EXC-NO CUT OFF POINT FOR HYPERGLYCAEMIA OR BLOOD GLUCOSE

Marano, L., Bestetti, A., Lomuscio, A., Tagliabue, L., Castini, D., Tarricone, D., Dario, P., Tarolo, G.L., & Fiorentini, C. 2000. Effects of infusion of glucose-insulin-potassium on myocardial function after a recent myocardial infarction. Acta Cardiologica, 55, (1) 9-15
Ref ID: 5804
EXC-NOT PERI ACS AND HYPERGLYCAEMIA AND NO EVALUATION OF BASELINE BLOOD GLUCOSE

Wistbacka, J.-O., Lepojarvi, M.V.K., Karlqvist, K.E.V., Koistinen, J., Kaukoranta, P.K., Nissinen, J., Peltola, T., Rainio, P., Ruokonen, A., & Nuutinen, L.S. 1995. Amino acid-enriched glucose-insulin-potassium infusion improves hemodynamic function after coronary bypass surgery. A double-blind study in patients with unstable angina and/or compromised left ventricular function. Infusionstherapie und Transfusionsmedizin, 22, (2) 82-90
Ref ID: 5996
EXC-PATIENTS UNDERGOING CABG

Pache, J., Kastrati, A., Mehilli, J., Bollwein, H., Ndrepepa, G., Schuhlen, H., Martinoff, S., Seyfarth, M., Nekolla, S., Dirschinger, J., Schwaiger, M., & and Schomig, A. A randomized evaluation of the effects of glucose-insulin-potassium infusion on myocardial salvage in patients with acute myocardial infarction treated with reperfusion therapy. American heart journal 148[1]. 2004.
Ref Type: Generic
Ref ID: 6048
EXC-NO PERI ACS AND HYPERGLYCAEMIA

The OASIS-6 trial group. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction The OASIS-6 randomized trial. JAMA 295[13], 1519-1530. 2006.
Ref Type: Generic
Ref ID: 6049

EXC-RESULTS FOR GIK INFUSION NOT REPORTED HERE. NOT PERI ACS AND HYPERGLYCAEMIA

Brunkhorst, F. M., Engel, C., Bloos, F., Meier-Hellmann, A., Ragaller, M., Weiler, N., Moerer, O., & et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. The New England journal of medicine 358, 125-139. 2008.
Ref Type: Generic
Ref ID: 6050
EXC-NOT SPECIFIC TO ACS

Van den Berghe, G., Wouters, P., Weekers, F., Verwaest, C., Bruyninckx, F., & et al. Intensive insulin therapy in critically ill patients. The New England journal of medicine 345[19], 1359-1367. 2001.
Ref Type: Generic
Ref ID: 6051
EXC-NOT SPECIFIC TO ACS

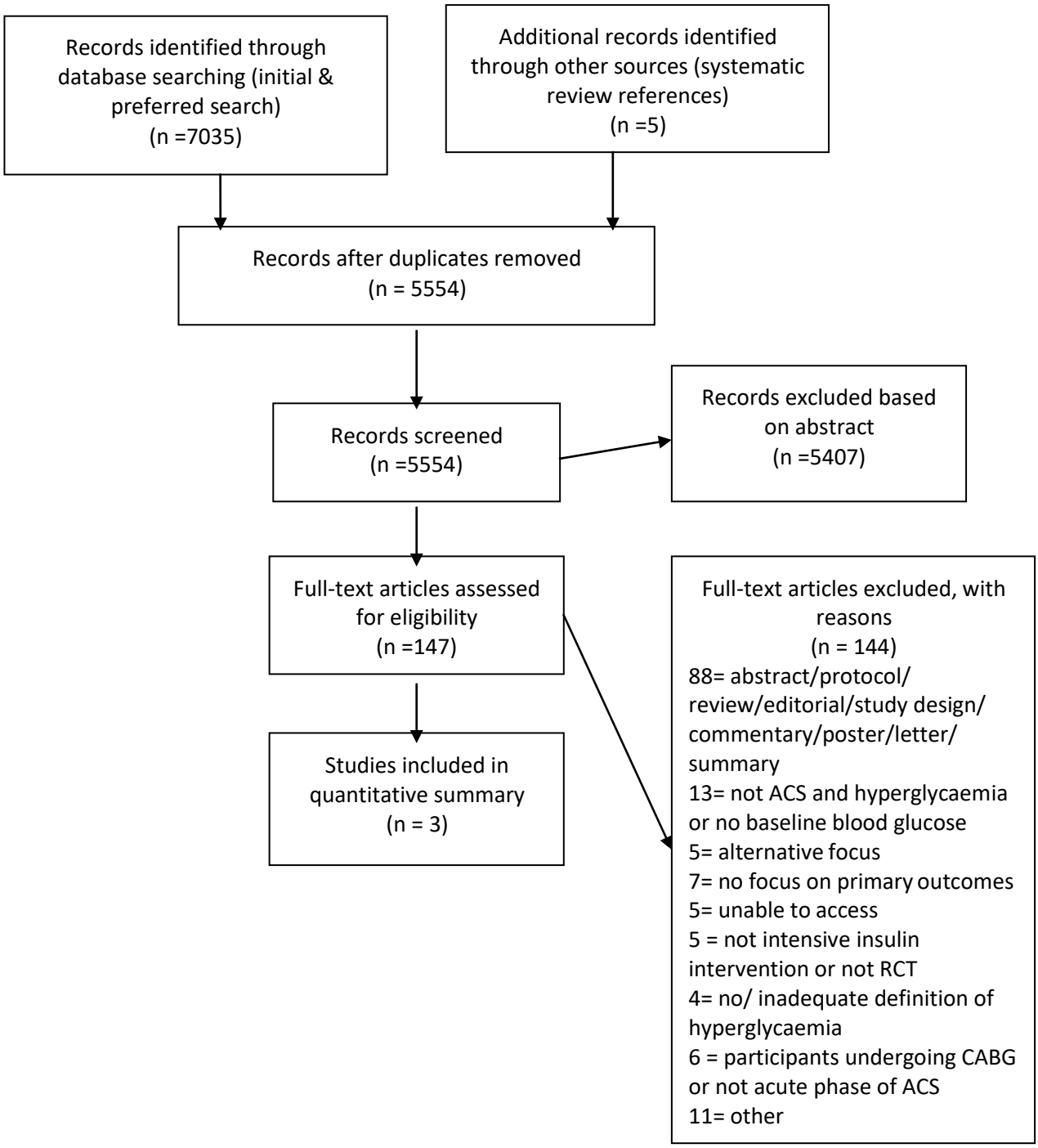
Van der Berghe, G., Wilmer, A., Hermans, G., Meersseman, W., & et al. Intensive insulin therapy in the medical ICU. The New England journal of medicine 354[5]. 2006.
Ref Type: Generic
Ref ID: 6052
EXC-NOT SPECIFIC TO ACS

Diaz, R., Paolasso, E.A., Piegas, L.S., Tajer, C.D., Moreno, M.G., Corvalan, R., Isea, J.E., & Romero, G. 1998. Metabolic modulation of acute myocardial infarction: The ECLA glucose- insulin-potassium pilot trial. Circulation, 98, (21) 2227-2234
Ref ID: 6013

EXC-NO DEFINITION OF HYPERGLYCAEMIA

## *Flow diagram of excluded studies for hyperglycaemia review Question 2*

The flow diagram below shows an overview of the studies that were identified, included and excluded for review question 2 which focuses on the metabolic management of patients with ACS and hyperglycaemia without diagnosed diabetes.



## *Excluded studies*

### List of excluded studies for review question 2 (non-diabetes)

Bianchi, C., Miccoli, R., Daniele, G., Penno, G., & Del, P.S. 2009. Is there evidence that oral hypoglycemic agents reduce cardiovascular morbidity/mortality? Yes. [Review] [53 refs]. Diabetes Care, 32, Suppl-8
Ref ID: 12A
EXC-NARRATIVE REVIEW

Mannucci, E., Monami, M., Lamanna, C., Gori, F., & Marchionni, N. 2009. Prevention of cardiovascular disease through glycemic control in type 2 diabetes: a meta-analysis of randomized clinical trials. Nutrition Metabolism & Cardiovascular Diseases, 19, (9) 604-612
Ref ID: 13A
EXC-REVIEW WITHOUT PERI ACS AND HYPERGLYCAEMIA AND FOCUS ON TYPE 2 DIABETES

Goyal, A., Mehta, S.R., Diaz, R., Gerstein, H.C., Afzal, R., Xavier, D., Liu, L., Pais, P., & Yusuf, S. 2009. Differential clinical outcomes associated with hypoglycemia and hyperglycemia in acute myocardial infarction. Circulation, 120, (24) 2429-2437
Ref ID: 15A
EXC-FOCUS ON PROGNOSTIC SIGNIFICANCE OF HYPERGLYCAEMIA ON ADMISSION

Avanzini, F., Marelli, G., Donzelli, W., Sorbara, L., Palazzo, E., Bellato, L., Colombo, E.L., Roncaglioni, M.C., Riva, E., De, M.M., & DDD study group 2009. Hyperglycemia during acute coronary syndrome: a nurse-managed insulin infusion protocol for stricter and safer control. European Journal of Cardiovascular Nursing, 8, (3) 182-189
Ref ID: 18A
EXC-PROTOCOL FOR INTENSIVE INSULIN AND NOT AN RCT

Monteiro, S., Monteiro, P., & Providencia, L.A. 2009. Optimization of blood glucose control in MI patients: state of the art and a proposed protocol for

intensive insulin therapy. [Review] [28 refs]. Revista Portuguesa de Cardiologia, 28, (1) 49-61
Ref ID: 22A
EXC-NARRATIVE REVEIW

Anantharaman, R., Heatley, M., & Weston, C.F. 2009. Hyperglycaemia in acute coronary syndromes: risk-marker or therapeutic target?. [Review] [65 refs]. Heart, 95, (9) 697-703
Ref ID: 26A
EXC-REVIEW

Gan, R.M., Wong, V., Cheung, N.W., & McLean, M. 2009. Effect of insulin infusion on electrocardiographic findings following acute myocardial infarction: importance of glycaemic control. Diabetic Medicine, 26, (2) 174-176
Ref ID: 30A
EXC-FOCUS ON ECG CHANGES AS AN OUTCOME

Goyal, A., Nerenberg, K., Gerstein, H.C., Umpierrez, G., & Wilson, P.W. 2008. Insulin therapy in acute coronary syndromes: an appraisal of completed and ongoing randomised trials with important clinical end points. [Review] [58 refs]. Diabetes & Vascular Disease Research, 5, (4) 276-284
Ref ID: 35A
EXC-REVIEW

Cheung, N.W. 2008. Glucose control during acute myocardial infarction. [Review] [20 refs]. Internal Medicine Journal, 38, (5) 345-348
Ref ID: 49A
EXC-NARRATIVE REVIEW

Braatvedt, G.D. 2008. Glucose control peri-myocardial infarction. [Review] [17 refs]. Internal Medicine Journal, 38, (5) 341-344
Ref ID: 50A
EXC-NARRATIVE REVIEW

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Timmer, J.R., van der Horst, I.C., Ottervanger, J.P., De, L.G., van 't Hof, A.W., Bilo, H.J., & Zijlstra, F. 2004. Glucose-insulin-potassium infusion as adjunctive therapy in myocardial infarction: current evidence and potential mechanisms. Italian Heart Journal: Official Journal of the Italian Federation of Cardiology, 5, (10) 727-731
Ref ID: 1682
EXC-REVIEW

Apstein, C.S. 2003. The benefits of glucose-insulin-potassium for acute myocardial infarction (and some concerns). [Review] [30 refs]. Journal of the American College of Cardiology, 42, (5) 792-795
Ref ID: 1796
EXC-EDITORIAL COMMENT

Janiger, J.L. & Cheng, J.W. 2002. Glucose-insulin-potassium solution for acute myocardial infarction. [Review] [14 refs]. Annals of Pharmacotherapy, 36, (6) 1080-1084
Ref ID: 1887
EXC-NARRATIVE REVIEW

Ceremuzynski, L., Budaj, A., Czepiel, A., Burzykowski, T., Achremczyk, P., Smielak-Korombel, W., Maciejewicz, J., Dziubinska, J., Nartowicz, E., Kawka-Urbanek, T., Piotrowski, W., Hanzlik, J., Cieslinski, A., Kawecka-Jaszcz, K., Gessek, J., & Wrabec, K. 1999. Low-dose glucose-insulin-potassium is ineffective in acute myocardial infarction: results of a randomized multicenter Pol-GIK trial. Cardiovascular Drugs & Therapy, 13, (3) 191-200
Ref ID: 2044
EXC-NO PERI ACS AND HYPERGLYCAEMIA

Apstein, C.S. & Opie, L.H. 1999. Glucose-insulin-potassium (GIK) for acute myocardial infarction: a negative study with a positive value. [Review] [38 refs]. Cardiovascular Drugs & Therapy, 13, (3) 185-189
Ref ID: 2045
EXC-EDITORIAL

Fath-Ordoubadi, F. & Beatt, K.J. 1999. Glucose-insulin-potassium in acute myocardial infarction. Lancet, 353, (9168) 1968
Ref ID: 2050
EXC-CORRESPONDENCE

Fisher, M. 1999. Diabetes and myocardial infarction. [Review] [56 refs]. Best Practice & Research Clinical Endocrinology & Metabolism, 13, (2) 331-343
Ref ID: 2078
EXC-NARRATIVE REVIEW

Apstein, C.S. 1998. Glucose-insulin-potassium for acute myocardial infarction: remarkable results from a new prospective, randomized trial. [Review] [27 refs]. Circulation, 98, (21) 2223-2226
Ref ID: 2102
EXC-EDITIORIAL

Williams, R. 1997. Intensive insulin treatment after acute myocardial infarction in diabetes mellitus. Evidence exists from study of non-insulin dependent diabetes in Japan. BMJ, 315, (7107) 544
Ref ID: 2168
EXC-EDITORIAL

Surawicz, B. 1968. Evaluation of treatment of acute myocardial infarction with potassium, glucose and insulin. [Review] [110 refs]. Progress in Cardiovascular Diseases, 10, (6) 545-560
Ref ID: 2692
EXC-NARRATIVE REVIEW

Rogers, W.J., McDaniel, H.G., Mantle, J.A., & Rackley, C.E. 1982. Glucose-insulin-potassium infusion in acute myocardial infarction - results of a prospective randomized study. Clinical Research, 30, (2) 216A
Ref ID: 2877
EXC-ABSTRACT ONLY

Stanley, J., Prather, J.W., & Snow, R.M. 1979. Glucose-insulin-potassium, acute myocardial infarction and patient mortality: Results from an ongoing prospective randomized study. Clinical Research, 27, (5) 734A
Ref ID: 2921
EXC-ABSTRACT ONLY

Puskarich, M., Jones, A., Kline, J., Runyon, M., & Trzeciak, S. 2009. Critical Care, Conference: 29th International Symposium on Intensive Care and Emergency Medicine Brussels Belgium. Conference Start: 20090324 Conference End: 20090327. Conference: 29th International Symposium on Intensive Care and Emergency Medicine Brussels Belgium. Conference Start: 20090324 Conference End: 20090327. Conference Publication: (var.pagings) S54
Ref ID: 3462
EXC-BRITISH LIBRARY CANNOT PROVIDE A COPY

Cefalu, W.T. & Watson, K. 2008. Intensive glycemic control and cardiovascular disease observations from the ACCORD study: Now what can a clinician possibly think? Diabetes, 57, (5) 1163-1165
Ref ID: 3525
EXC-EDITORIAL

Goyal, A., Nerenberg, K., Gerstein, H.C., Umpierrez, G., & Wilson, P.W.F. 2008. Insulin therapy in acute coronary syndromes: An appraisal of completed

and ongoing randomised trials with important clinical end points. Diabetes and Vascular Disease Research, 5, (4) 276-284
Ref ID: 3585
EXC-REVIEW

Goyal, A., Diaz, R., & Mehta, S.R. 2008. Glucose-insulin-potassium therapy in patients with STEMI: Reply. JAMA - Journal of the American Medical Association, 299, (20) 2387-2388
Ref ID: 3696
EXC-LETTER

Opie, L.H. 2008. Glucose-insulin-potassium therapy in patients with STEMI [2]. JAMA - Journal of the American Medical Association, 299, (20) 2385-2386
Ref ID: 3697
EXC-LETTER

Ranasinghe, A.M., Quinn, D.W., Pagano, D., Edwards, N., Faroqui, M., Graham, T.R., Keogh, B.E., Mascaro, J., Riddington, D.W., Rooney, S.J., Townend, J.N., Wilson, I.C., & Bonser, R.S. 2006. Glucose-insulin-potassium and tri-iodothyronine individually improve hemodynamic performance and are associated with reduced troponin I release after on-pump coronary artery bypass grafting. Circulation, 114, (SUPPL. 1) I245-I250
Ref ID: 4253
EXC-PARTCIPANTS UNDERGOING CABG

Yazici, M., Demircan, S., Durna, K., Yasar, E., Acar, Z., & Sahin, M. 2005. Effect of glucose-insulin-potassium infusion on myocardial damage due to percutaneous coronary revascularization. American Journal of Cardiology, 96, (11) 1517-1520
Ref ID: 4456
EXC-NO FOCUS ON PRIMARY OUTCOMES

2005. Effect of glucose-insulin-potassium infusion on mortality in patients with acute ST-segment elevation myocardial infarction: Comments. Indian Heart Journal, 57, (2) 187

Ref ID: 4535
EXC-COMMENT

van der Horst, I.C.C., De, L.G., Ottervanger, J.P., de, B.M.J., Hoorntje, J.C.A., Suryapranata, H., Dambrink, J.-H., Gosselink, A.T.M., Zijlstra, F., & Van 't Hof, A.W.J. 2005. ST-segment elevation resolution and outcome in patients treated with primary angioplasty and glucose-insulin-potassium infusion. American heart journal, 149, (6) 1135
Ref ID: 4555
EXC-NOT PERI ACS AND HYPERGLYCAEMIA AND NO EVALUATION OF BASELINE BLOOD GLUCOSE

van der Horst, I.C.C., Timmer, J.R., Ottervanger, J.P., Bilo, H.J.G., Gans, R.O.B., de, B.M.J., & Zijlstra, F. 2005. Glucose-insulin-potassium and reperfusion in acute myocardial infarction: Rationale and design of the Glucose-Insulin-Potassium Study-2 (GIPS-2). American heart journal, 149, (4) 585-591
Ref ID: 4601
EXC-NO MENTION OF BASELINE BLOOD GLUCOSE

Zhang, L., Li, Y.H., Zhang, H.Y., Chen, M.L., Gao, M.-M., Hu, A.H., Yang, H.S., & Liu, L.S. 2005. High-dose glucose-insulin-potassium treatment reduces myocardial apoptosis in patients with acute myocardial infarction. European journal of clinical investigation, 35, (3) 164-170
Ref ID: 4630
EXC-NOT PERI ACS AND HYPERGLYCAEMIA AND NO EVALUATION OF BASELINE BLOOD GLUCOSE

Yusuf, S., Mehta, S.R., Diaz, R., Paolasso, E., Pais, P., Xavier, D., Xie, C., Ahmed, R.J., Khazmi, K., Zhu, J., & Liu, L. 2004. Challenges in the conduct of large simple trials of important generic questions in resource-poor settings: The CREATE and ECLA trial program evaluating GIK (glucose, insulin and potassium) and low-molecular-weight heparin in acute myocardial infarction. American heart journal, 148, (6) 1068-1078

Ref ID: 4705
EXC-RELATES TO STUDY DESIGN

Kastrati, A. & Bellandi, F. 2004. Trial finds routine intravenous glucose-insulin-potassium does not improve myocardial salvage in people with acute myocardial infarction. Evidence-based Cardiovascular Medicine, 8, (4) 339-342
Ref ID: 4707
EXC-NOT PERI ACS AND HYPERGLYCAEMIA

Lazar, H.L., Chipkin, S.R., Fitzgerald, C.A., Bao, Y., Cabral, H., & Apstein, C.S. 2004. Tight Glycemic Control in Diabetic Coronary Artery Bypass Graft Patients Improves Perioperative Outcomes and Decreases Recurrent Ischemic Events. Circulation, 109, (12) 1497-1502
Ref ID: 4850
EXC-PARTICIPANTS UNDERGOING CABG

Castro, P.F., Larrain, G., Baeza, R., Corbalan, R., Nazzal, C., Greig, D.P., Miranda, F.P., Perez, O., Acevedo, M., Marchant, E., Olea, E., & Gonzalez, R. 2003. Effects of glucose-insulin-potassium solution on myocardial salvage and left ventricular function after primary angioplasty. Critical care medicine, 31, (8) 2152-2155
Ref ID: 5004
EXC-NOT PERI ACS AND HYPERGLYCAEMIA

Stefanidis, A., Melidonis, A., Tournis, S., Zairis, M., Handanis, S., Olympios, C., Asimacopoulos, P., & Foussas, S. 2002. Intensive insulin treatment reduces transient ischaemic episodes during acute coronary events in diabetic patients. Acta Cardiologica, 57, (5) 357-364
Ref ID: 5150
EXC-HYPERGLYCAEMIC POPULATION NOT WELL DEFINED AND DOES NOT DEFINE BLOOD GLUCOSE ON RECRUITMENT

Diaz-Araya, G., Nettle, D., Castro, P., Miranda, F., Greig, D., Campos, X., Chiong, M., Nazzal, C., Corbalan, R., & Lavandero, S. 2002. Oxidative stress after reperfusion with primary coronary angioplasty: Lack of effect of glucose-

insulin-potassium infusion. Critical care medicine, 30, (2) 417-421
Ref ID: 5220
EXC-NOT PERI ACS AND HYPERGLYCAEMIA AND OXIDATIVE STRESS NOT A PRIMARY OUTCOME

Fath-Ordoubadi, F., Markides, V., & Beatt, K.J. 1998. Meta-analysis of glucose-insulin-potassium therapy for myocardial infarction. Cardiology Review, 15, (4) 41-44
Ref ID: 5511
EXC-REVIEW ARTICLE NOT FOCUSING ON PERI ACS AND HYPERGLYCAEMIA

Fath-Ordoubadi, F. & Beatt, K.J. 1997. Glucose-insulin-potassium therapy for treatment of acute myocardial infarction: An overview of randomized placebo-controlled trials. Circulation, 96, (4) 1152-1156
Ref ID: 5571
EXC-REVIEW

Mellbin, L.G., Malmberg, K., Norhammar, A., Wedel, H., & Ryden, L. 2008. The impact of glucose lowering treatment on long-term prognosis in patients with type 2 diabetes and myocardial infarction: A report from the DIGAMI 2 trial. European heart journal, 29, (2) 166-176
Ref ID: 5618
EXC-FOCUS ON TREATMENT FOLLOWING DISCHARGE (NOT ACUTE PHASE)

Rasoul, S., Ottervanger, J.P., Timmer, J.R., Svilaas, T., Henriques, J.P.S., Dambrink, J.-H., van der Horst, I.C.C., & Zijlstra, F. 2007. One year outcomes after glucose-insulin-potassium in ST elevation myocardial infarction. The Glucose-insulin-potassium study II. International journal of cardiology, 122, (1) 52-55
Ref ID: 5703
EXC-NO CUT OFF POINT FOR HYPERGLYCAEMIA OR BLOOD GLUCOSE

Marano, L., Bestetti, A., Lomuscio, A., Tagliabue, L., Castini, D., Tarricone, D., Dario, P., Tarolo, G.L., & Fiorentini, C. 2000. Effects of infusion of glucose-

insulin-potassium on myocardial function after a recent myocardial infarction. Acta Cardiologica, 55, (1) 9-15
Ref ID: 5804
EXC-NOT PERI ACS AND HYPERGLYCAEMIA AND NO EVALUATION OF BASELINE BLOOD GLUCOSE

Wistbacka, J.-O., Lepojarvi, M.V.K., Karlqvist, K.E.V., Koistinen, J., Kaukoranta, P.K., Nissinen, J., Peltola, T., Rainio, P., Ruokonen, A., & Nuutinen, L.S. 1995. Amino acid-enriched glucose-insulin-potassium infusion improves hemodynamic function after coronary bypass surgery. A double-blind study in patients with unstable angina and/or compromised left ventricular function. Infusionstherapie und Transfusionsmedizin, 22, (2) 82-90
Ref ID: 5996
EXC-PATIENTS UNDERGOING CABG

Pache, J., Kastrati, A., Mehilli, J., Bollwein, H., Ndrepepa, G., Schuhlen, H., Martinoff, S., Seyfarth, M., Nekolla, S., Dirschinger, J., Schwaiger, M., & and Schomig, A. A randomized evaluation of the effects of glucose-insulin-potassium infusion on myocardial salvage in patients with acute myocardial infarction treated with reperfusion therapy. American heart journal 148[1]. 2004.
Ref Type: Generic
Ref ID: 6048
EXC-NO PERI ACS AND HYPERGLYCAEMIA

The OASIS-6 trial group. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction The OASIS-6 randomized trial. JAMA 295[13], 1519-1530. 2006.
Ref Type: Generic
Ref ID: 6049
EXC-RESULTS FOR GIK INFUSION NOT REPORTED HERE. NOT PERI ACS AND HYPERGLYCAEMIA

Brunkhorst, F. M., Engel, C., Bloos, F., Meier-Hellmann, A., Ragaller, M., Weiler, N., Moerer, O., & et al. Intensive insulin therapy and pentastarch

resuscitation in severe sepsis. The New England journal of medicine 358, 125-139. 2008.
Ref Type: Generic
Ref ID: 6050
EXC-NOT SPECIFIC TO ACS

Van den Berghe, G., Wouters, P., Weekers, F., Verwaest, C., Bruyninckx, F., & et al. Intensive insulin therapy in critically ill patients. The New England journal of medicine 345[19], 1359-1367. 2001.
Ref Type: Generic
Ref ID: 6051
EXC-NOT SPECIFIC TO ACS

Van der Berghe, G., Wilmer, A., Hermans, G., Meersseman, W., & et al. Intensive insulin therapy in the medical ICU. The New England journal of medicine 354[5]. 2006.
Ref Type: Generic
Ref ID: 6052
EXC-NOT SPECIFIC TO ACS

Diaz, R., Paolasso, E.A., Piegas, L.S., Tajer, C.D., Moreno, M.G., Corvalan, R., Isea, J.E., & Romero, G. 1998. Metabolic modulation of acute myocardial infarction: The ECLA glucose- insulin-potassium pilot trial. Circulation, 98, (21) 2227-2234
Ref ID: 6013

EXC-NO DEFINITION OF HYPERGLYCAEMIA

Malmberg, K., Rydén, L., Efendic, S., Herlitz, J., Nicol, P., Waldenström, A., Wedel, H., & Welin, L. 1995. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. Journal of the American College of Cardiology, 26, (1) 57-65
Ref ID: 396
EXC-ASSESSED FOR RQ1 (PATIENTS WITH DIABETES)

Malmberg, K., Rydén, L., Hamsten, A., Herlitz, J., Waldenström, A., & Wedel, H. 1996. Effects of insulin treatment on cause-specific one-year mortality and morbidity in diabetic patients with acute myocardial infarction. DIGAMI Study Group. Diabetes Insulin-Glucose in Acute Myocardial Infarction. European heart journal, 17, (9) 1337-1344
Ref ID: 378
EXC-ASSESSED FOR RQ1 (PATIENTS WITH DIABETES)

Malmberg, K., Ryden, L., Hamsten, A., Herlitz, J., Waldenstrom, A., & Wedel, H. 1997. Mortality prediction in diabetic patients with myocardial infarction: experiences from the DIGAMI study.[Erratum appears in Cariovasc Res 1997 Dec;36(3):460]. Cardiovascular research, 34, (1) 248-253
Ref ID: 2181
EXC-ASSESSED FOR RQ1 (PATIENTS WITH DIABETES)

Malmberg, K. 1997. Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) Study Group. BMJ (Clinical research ed.), 314, (7093) 1512-1515
Ref ID: 367
EXC-ASSESSED FOR RQ1 (PATIENTS WITH DIABETES)

Mellbin, L.G., Malmberg, K., Waldenstrom, A., Wedel, H., & Ryden, L. 2009. Prognostic implications of hypoglycaemic episodes during hospitalisation for myocardial infarction in patients with type 2 diabetes: A report from the DIGAMI 2 trial. Heart, 95, (9) 721-727
Ref ID: 3363
EXC-ASSESSED FOR RQ1 (PATIENTS WITH DIABETES)

Malmberg, K. 2004. Role of insulin-glucose infusion in outcomes after acute myocardial infarction: the diabetes and insulin-glucose infusion in acute myocardial infarction (DIGAMI) study. Endocrine Practice, 10, Suppl-6
Ref ID: 144
EXC-ASSESSED FOR RQ1 (PATIENTS WITH DIABETES)

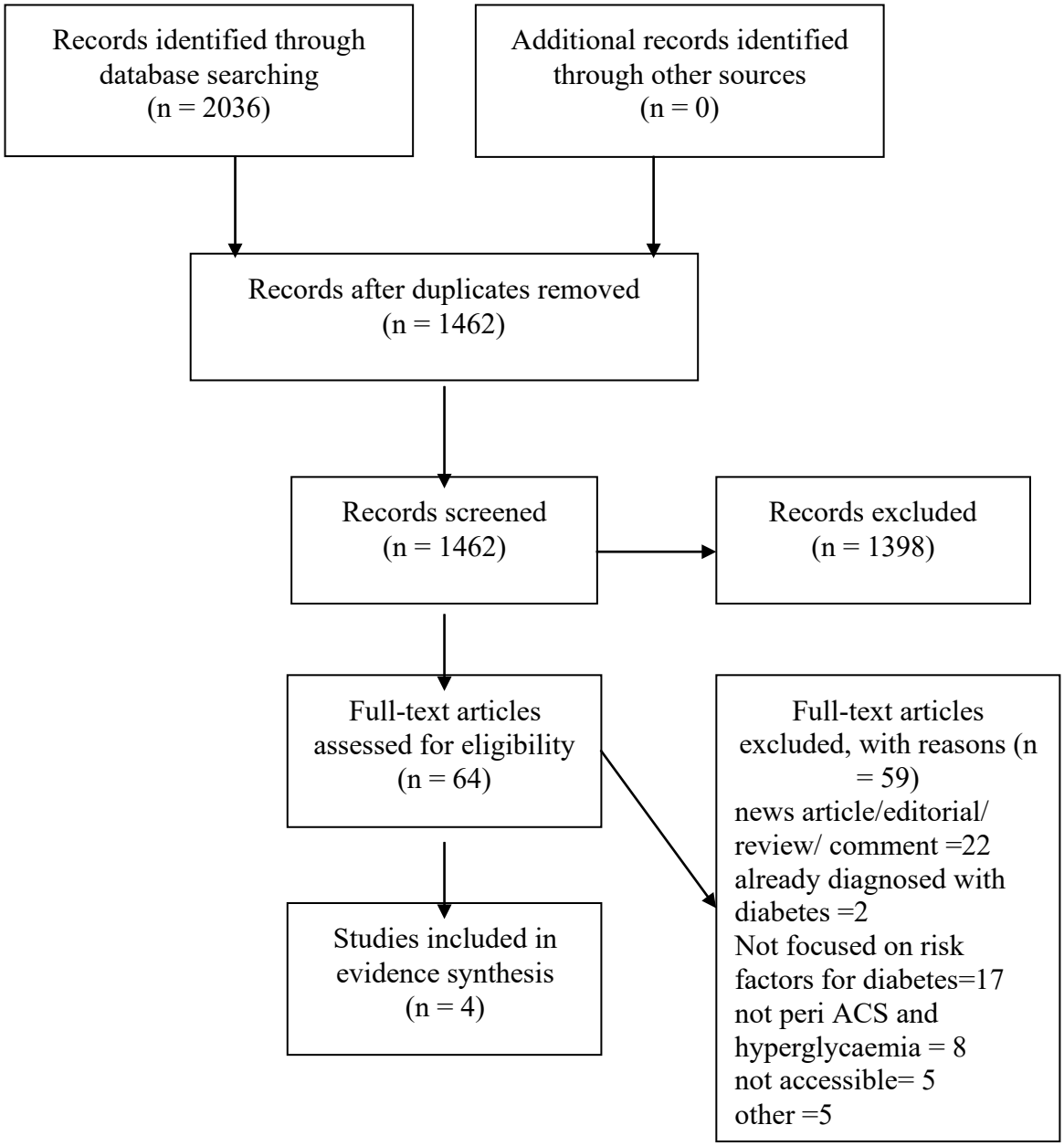
Malmberg, K., Norhammar, A., Wedel, H., & Ryden, L. 1999. Glycometabolic state at admission: important risk marker of mortality in conventionally treated patients with diabetes mellitus and acute myocardial infarction: long-term results from the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study. Circulation, 99, (20) 2626-2632
Ref ID: 207
EXC-ASSESSED FOR RQ1 (PATIENTS WITH DIABETES)

Malmberg, K., Ryd+®n, L., Wedel, H., Birkeland, K., Bootsma, A., Dickstein, K., Efendic, S., Fisher, M., Hamsten, A., Herlitz, J., Hildebrandt, P., MacLeod, K., Laakso, M., Torp-Pedersen, C., & Waldenstr+Âm, A. 2005. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. European heart journal, 26, (7) 650-661 available from: http://eurheartj.oxfordjournals.org/content/26/7/650.abstract
Ref ID: 6053

EXC-ASSESSED FOR RQ1 (PATIENTS WITH DIABETES)

### *Flow diagram of excluded studies for hyperglycaemia review question 3*

The flow diagram below shows an overview of the studies that were identified, included and excluded for review question 3, which focuses on risk factors for diabetes in patients with ACS and hyperglycaemia.



## *Excluded studies*

### Full list of excluded studies for RQ3-Risk factors for diabetes

2007. Newsline: another risk factor turns up for diabetes. Clinical Advisor for Nurse Practitioners, 10, (10) 11-12
Ref ID: 1964
EXCLUDE-NEWS ARTICLE

Adler, A.I., Neil, H.A.W., Manley, S.E., Holman, R.R., & Turner, R.C. 1999. Hyperglycemia and hyperinsulinemia at diagnosis of diabetes and their association with subsequent cardiovascular disease in the United Kingdom Prospective Diabetes Study (UKPDS 47). American Heart Journal, 138, (5 I) S353-S359
Ref ID: 1100
EXCLUDE-PARTICIPANTS ALREADY DIAGNOSED WITH DIABETES

Alajbegovic, S., Metelko, Z., Alajbegovic, A., Suljic, E., & Resic, H. 2003. Hyperglycemia and acute myocardial infarction in a nondiabetic population. Diabetologia Croatica, 32, (4) 169-174
Ref ID: 905
EXCLUDE-FOCUS ON PREVALANCE OF DIABETES NOT RISK FACTORS FOR ITS DEVELOPMENT

Aquilante, C.L. & Griend, J.R.V. 2008. Understanding metabolic syndrome: Knowing the risks. Pharmacy Times, 74, (7) 61-68
Ref ID: 386
EXCLUDE-REVIEW

Bangalore, S., Parkar, S., Grossman, E., & Messerli, F.H. 2007. A meta-analysis of 94,492 patients with hypertension treated with beta blockers to determine the risk of new-onset diabetes mellitus. American Journal of Cardiology, 100, (8) 1254-1262
Ref ID: 1902
EXCLUDE-NOT PERI ACS AND HYPERGLYCAEMIA

Barry, H. 2002. How often does diabetes occur within 3 months of an acute myocardial infarction? Evidence-Based Practice, 5, (10) -NaN
Ref ID: 2023
EXCLUDE-NOT ACCESSIBLE

Basile, J.N. 2009. Antihypertensive therapy, new-onset diabetes, and cardiovascular disease. International Journal of Clinical Practice, 63, (4) 656-666
Ref ID: 211
EXCLUDE-REVIEW ARTICLE

Belknap, S. 2008. Review: beta-blockers for hypertension increase risk of new onset diabetes: Commentary. Evidence-Based Medicine, 13, (2) 50
Ref ID: 418
EXCLUDE-NOT PERI ACS AND HYPERGLYCAEMIA

Bestermann, W., Houston, M.C., Basile, J., Egan, B., Ferrario, C.M., Lackland, D., Hawkins, R.G., Reed, J., Rogers, P., Wise, D., & Moore, M.A. 2005. Addressing the global cardiovascular risk of hypertension, dyslipidemia, diabetes mellitus, and the metabolic syndrome in the Southeastern United States, part II: Treatment recommendations for management of the global cardiovascular risk of hypertension, dyslipidemia, diabetes mellitus, and the metabolic syndrome. American Journal of the Medical Sciences, 329, (6) 292-305
Ref ID: 769
EXCLUDE-REVIEW FOCUSING ON CARDIOVASCULAR RISK

Betteridge, D.J. 2004. The interplay of cardiovascular risk factors in the metabolic syndrome and type 2 diabetes. European Heart Journal, Supplement, 6, (7) G3-G7
Ref ID: 828
EXCLUDE-REVIEW FOCUSING ON RISK OF CARDIOVASCULAR DISEASE

Braatvedt, G.D. 2008. Glucose control peri-myocardial infarction. Internal Medicine Journal, 38, (5) 341-344

Ref ID: 415
EXCLUDE-REVIEW FOCUSING ON EFFECT ON MORTALITY

Brancati, F. 2000. Resolving the glucose response curve: The underestimated importance of postprandial glucose. American Journal of Managed Care, 6, (21 SUPPL.) S1082-S1088
Ref ID: 1071
EXCLUDE-FOCUS ON RISK OF MORTALITY

Califf, R.M., Boolell, M., Haffner, S.M., Bethel, M.A., McMurray, J., Duggal, A., & Holman, R.R. 2008. Prevention of diabetes and cardiovascular disease in patients with impaired glucose tolerance: Rationale and design of the Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) Trial. American Heart Journal, 156, (4) 623-632
Ref ID: 369
EXCLUDE-DETAILS OF TRIAL DESIGN

Capes, S.E., Hunt, D., Malmberg, K., & Gerstein, H.C. 2000. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: A systematic overview. Lancet, 355, (9206) 773-778
Ref ID: 1093
EXCLUDE-FOCUS ON RISK OF MORTALITY NOT PROGRESSION TO DIABETES

Chioncel, V., Mincu, D., Anastasiu, M., & Sinescu, C. 2009. The prognostic value of blood glucose level on admission in non-diabetic patients with acute myocardial infarction. Journal of medicine and life, 2, (3) 271-278
Ref ID: 51
EXCLUDE-NO FOCUS ON DEVELOPMENT OF DIABETES

Colagiuri, S., Cull, C.A., & Holman, R.R. 2002. Are lower fasting plasma glucose levels at diagnosis of type 2 diabetes associated with improved outcomes?: U.K. prospective diabetes study 61. Diabetes Care, 25, (8) 1410-1417

Ref ID: 996
EXCLUDE-PATIENTS ALREADY DIAGNOSED WITH TYPE 2 DIABETES

Conaway, D.G. & O'Keefe, J.H. 2006. Frequency of undiagnosed and untreated diabetes mellitus in patients with acute coronary syndromes. Expert Review of Cardiovascular Therapy, 4, (4) 503-507
Ref ID: 647
EXCLUDE-NARRATIVE REVIEW

Davis, T.M.E. & Colagiuri, S. 2004. The continuing legacy of the United Kingdom prospective diabetes study. Medical Journal of Australia, 180, (3) 104-105
Ref ID: 895
EXCLUDE-EDITORIAL WITH NO FOCUS ON SUBSEQUENT DEVLEOPMENT OF DIABETES

Del, P.S., Bianchi, C., Miccoli, R., & Penno, G. 2007. Pharmacological intervention in prediabetes: Considering the risks and benefits. Diabetes, Obesity and Metabolism, 9, (SUPPL.1) 17-22
Ref ID: 501
EXCLUDE-REVIEW NOT FOCUSING ON PERI ACS AND HYPERGLYCAEMIA

Edavalath, M. & Rees, A. 2009. Therapy and clinical trials: Glycaemic control and cardiovascular disease. Current Opinion in Lipidology, 20, (6) 530-531
Ref ID: 66
EXCLUDE-COMMENT

Edelman, L., McGinn, T., & Korenstein, D. 2009. Just a spoonful of sugar: does presenting hyperglycemia impact prognosis in non-diabetics with acute myocardial infarction? Mount Sinai Journal of Medicine, 76, (3) 294-296
Ref ID: 1295
EXCLUDE-NOT FOCUSED ON RISK FACTORS FOR DIABETES

Engberg, S., Vlstisen, D., Lau, C., Glumer, C., Joorgensen, T., Pedersen, O., & Borch-Johnsen, K. 2009. Progression to impaired glucose regulation and

diabetes in the population-based inter99 study. Diabetes Care, 32, (4) 606-611
Ref ID: 167
EXCLUDE-PATIENTS FROM GENERAL POPULATION WITH HYPERGLYCAEMIA WITHOUT ACS. HIGH RISK GROUP HAVE ABSOLUTE RISK OF ISCHEMIC HEART DISEASE

Fisman, E.Z., Motro, M., Tenenbaum, A., Boyko, V., Mandelzweig, L., & Behar, S. 2001. Impaired fasting glucose concentrations in nondiabetic patients with ischemic heart disease: a marker for a worse prognosis. American Heart Journal, 141, (3) 485-490
Ref ID: 1664
EXCLUDE-FOCUS ON PREDICTORS OF MORTALITY

Fonseca, V. 2006. Newly diagnosed diabetes/hyperglycemia in hospitals: What should we do? Endocrine Practice, 12, (SUPPL. 3) 108-111
Ref ID: 599
ASSESS FOR RQ4 (PATIENT INFO)

Goyal, A., Mahaffey, K.W., Garg, J., Nicolau, J.C., Hochman, J.S., Weaver, W.D., Theroux, P., Oliveira, G.B.F., Todaro, T.G., Mojcik, C.F., Armstrong, P.W., & Granger, C.B. 2006. Prognostic significance of the change in glucose level in the first 24 h after acute myocardial infarction: Results from the CARDINAL study. European Heart Journal, 27, (11) 1289-1297
Ref ID: 667
EXCLUDE-FOCUS ON RISK OF MORTALITY NOT PROGRESSION TO DIABETES

Guptha, S.H., Suman, S., & Matthews, A.A. 2004. Screening for diabetes in medical inpatients with hyperglycaemia. Postgraduate Medical Journal, 80, (943) 302
Ref ID: 871
EXCLUDE-LETTER

Hanna-Moussa, A., Gardner, M.J., Romayne, K.L., & Sowers, J.R. 2009. Dysglycemia/prediabetes and cardiovascular risk factors. Reviews in

Cardiovascular Medicine, 10, (4) 202-208
Ref ID: 12
EXCLUDE-REVIEW FOCUSING ON RISK FACTORS FOR CARDIOVASCULAR DISEASE NOT PROGRESSION TO DIABETES

Herman, W.H., Hoerger, T.J., Hicks, K., Brandle, M., Sorensen, S.W., Zhang, P., Engelgau, M.M., Hamman, R.F., Marrero, D.G., Ackermann, R.T., & Ratner, R.E. 2006. Managing people at high risk for diabetes [4]. Annals of Internal Medicine, 144, (1) 66-67
Ref ID: 587
EXCLUDE-LETTER

Hristova, K., Milanov, S., & Petrov, D. 2010. Circulation, Conference: World Congress of Cardiology Scientific Sessions 2010, WCC 2010 Beijing China. Conference Start: 20100616 Conference End: 20100619. Conference: World Congress of Cardiology Scientific Sessions 2010, WCC 2010 Beijing China. Conference Start: 20100616 Conference End: 20100619. Conference Publication: (var.pagings) e195
Ref ID: 276
EXCLUDE-CONFERENCE PAPER

Husband, D.J., Alberti, K.G.M.M., & Julian, D.G. 1983. 'Stress' hyperglycaemia during acute myocardial infarction: An indicator of pre-existing diabetes. Lancet, 2, (8343) 179-181
Ref ID: 1231
EXCLUDE-NOT FOCUSED ON RISK FACTORS FOR DEVLEOPMENT OF DIABETES

Inzucchi, S.E. 2008. Hyperglycaemia and its therapy during acute coronary syndromes. Diabetes and Vascular Disease Research, 5, (4) 259
Ref ID: 358
EXCLUDE-EDITORIAL

Jessani, S., Gangopadhyay, K., Patel, J.V., Lip, G.Y., & Millane, T. 2007. Should oral glucose tolerance testing be mandatory following acute myocardial infarction? International Journal of Clinical Practice , 61, (4) 680-

683
Ref ID: 1403
EXCLUDE-NO FOCUS ON RISK FACTORS FOR THE DEVELOPMENT OF DIABETES

Klein, B.E., Klein, R., & Lee, K.E. 2002. Components of the metabolic syndrome and risk of cardiovascular disease and diabetes in beaver dam. Diabetes Care, 25, (10) 1790-1794
Ref ID: 990
EXCLUDE-DATA FOR PROGRESSION TO DIABETES IN PATIENTS WITH ELEVATED GLYCAEMIA BUT NO ACS

Lakhdar, A. 1998. The diagnosis of preexisting diabetes associated with acute myocardial infarction. Diabetes Care, 21, (3) 461
Ref ID: 1108
EXCLUDE-LETTER

Lavernia, F. 2008. Treating hyperglycemia and diabetes with insulin therapy: Transition from inpatient to outpatient care. MedGenMed Medscape General Medicine, 10, (9)
Ref ID: 374
EXCLUDE-NOT ACCESSIBLE

Madsen, J.K., Haunsoe, S., & Helquist, S. 1986. Prevalence of hyperglycaemia and undiagnosed diabetes mellitus in patients with acute myocardial infarction. Acta Medica Scandinavica, 220, (4) 329-332
Ref ID: 1214
EXCLUDE-FOCUS ON PREVALANCE OF DIABETES NOT RISK FACTORS FOR PROGRESSION TO DIABETES

Melidonis, A., Koutsovasilis, A., Tsourous, G., Nikolaou, A., Chrysomallis, I., Dragoumanos, V., Iraklianou, S., & Foussas, S. 2010. Diabetologia, Conference: 46th Annual Meeting of the European Association for the Study of Diabetes, EASD 2010 Stockholm Sweden. Conference Start: 20100920 Conference End: 20100924. Conference: 46th Annual Meeting of the European Association for the Study of Diabetes, EASD 2010 Stockholm

Sweden. Conference Start: 20100920 Conference End: 20100924. Conference Publication: (var.pagings) S495
Ref ID: 299
EXCLUDE-CONFERENCE ABSTRACT

Monteiro, S., Monteiro, P., Goncalves, F., Freitas, M., & Providencia, L.A. 2010. Hyperglycaemia at admission in acute coronary syndrome patients: Prognostic value in diabetics and non-diabetics. European Journal of Cardiovascular Prevention and Rehabilitation, 17, (2) 155-159
Ref ID: 8
EXCLUDE-FOCUS ON RISK OF MORTALITY NOT PROGRESSION TO DIABETES

Mozaffarian, D., Marfisi, R., Levantesi, G., Silletta, M.G., Tavazzi, L., Tognoni, G., Valagussa, F., & Marchioli, R. 2007. Incidence of new-onset diabetes and impaired fasting glucose in patients with recent myocardial infarction and the effect of clinical and lifestyle risk factors. Lancet, 370, (9588) 667-675
Ref ID: 1388
EXCLUDE-FOCUSED ON RISK FACTORS FOR PROGRESSION TO DIABETES IN PATIENTS WITH ACS (NO SPECIFIC REFERENCE TO BASELINE BLOOD GLUCOSE)

Nesto, R.W. 2006. Prevalence of newly diagnosed diabetes in clinical settings. Reviews in Cardiovascular Medicine, 7, (SUPPL. 2) S18-S24
Ref ID: 582
EXCLUDE-REVIEW FOCUSING ON PREVALENCE OF DIABETES NOT RISK FACTORS FOR DEVELOPMENT OF DIABETES

Nichols, G.A., Koro, C.E., & Kolatkar, N.S. 2007. The epidemiology of congestive heart failure in hyperglycemia below the threshold for diabetes: A critical review. Diabetes and Metabolic Syndrome: Clinical Research and Reviews, 1, (4) 273-278
Ref ID: 486
EXCLUDE-REVIEW FOCUSING ON RISK OF CHRONIC HEART DISEASE

Nielson, C., Lange, T., & Hadjokas, N. 2006. Blood glucose and coronary artery disease in nondiabetic patients. Diabetes Care, 29, (5) 998-1001
Ref ID: 657
EXCLUDE-PATIENTS WITH HYPERGLYCAEMIA NOT INCLUDED

Nilsson, P.M. 2010. ACCORD and risk-factor control in type 2 diabetes. New England Journal of Medicine, 362, (17) 1628-1630
Ref ID: 11
EXCLUDE-EDITORIAL AND PATIENTS ALREADY DIAGNOSED WITH DIABETES

Oswald, G.A., Corcoran, S., & Yudkin, J.S. 1984. Prevalence and risks of hyperglycaemia and undiagnosed diabetes in patients with acute myocardial infarction. Lancet, 1, (8389) 1264-1267
Ref ID: 1223
EXCLUDE-NOT FOCUSED ON RISK FACTORS FOR PROGRESSION TO DIABETES

Oswald, G.A. & Yudkin, J.S. 1987. Hyperglycaemia following acute myocardial infarction: The contribution of undiagnosed diabetes. Diabetic Medicine, 4, (1) 68-70
Ref ID: 1200
EXCLUDE-TEMPORARILY UNAVAILABLE

Petursson, P., Herlitz, J., Caidahl, K., From-Attebring, M., Sjoland, H., Gudbjornsdottir, S., & Hartford, M. 2006. Association between glycometabolic status in the acute phase and 2 1/2 years after an acute coronary syndrome. Scandinavian Cardiovascular Journal, 40, (3) 145-151
Ref ID: 644
EXCLUDE-NOT SPECIFIC TO PROGRESSION TO DIABETES. FOCUSES ON GLYCOMETABOLIC DISTURBANCE IN GENERAL WHICH INCLUDES BOTH IFG OR DIABETES

Rasmussen, S.S., Lauritzen, T., Sandbaeck, A., & Borch-Johnsen, K. 2009. Diabetologia, Conference: 45th EASD Annual Meeting of the European Association for the Study of Diabetes Vienna Austria. Conference Start:

20090930 Conference End: 20091002. Conference: 45th EASD Annual Meeting of the European Association for the Study of Diabetes Vienna Austria. Conference Start: 20090930 Conference End: 20091002. Conference Publication: (var.pagings) S327
Ref ID: 109
EXCLUDE-CONFERENCE PAPER

Ravid, M., Berkowicz, M., & Sohar, E. 1975. Hyperglycemia during acute myocardial infarction. A six-year follow-up study. JAMA : the journal of the American Medical Association, 233, (7) 807-809
Ref ID: 1239
EXCLUDE-FOCUSED ON PREVALANCE OF DIABETES NOT RISK FACTORS FOR PROGRESSION TO DIABETES

Ryden, L., Standl, E., Bartnik, M., Van Den Berghe, G., Betteridge, J., De, B.M.J., Cosentino, F., Jonsson, B., Laakso, M., Malmberg, K., Priori, S., Ostergren, J., Tuomilehto, J., Thrainsdottir, I., Vanhorebeek, I., Stramba-Badiale, M., Lindgren, P., Qiao, Q., Priori, S.G., Blanc, J.-J., Budaj, A., Camm, J., Dean, V., Deckers, J., Dickstein, K., Lekakis, J., McGregor, K., Metra, M., Morais, J., Osterspey, A., Tamargo, J., Zamorano, J.L., Deckers, J.W., Bertrand, M., Charbonnel, B., Erdmann, E., Ferrannini, E., Flyvbjerg, A., Gohlke, H., Juanatey, J.R.G., Graham, I., Monteiro, P.F., Parhofer, K., Pyorala, K., Raz, I., Schernthaner, G., Volpe, M., & Wood, D. 2007. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: Full text. Diabetes, Stoffwechsel und Herz, 16, (7) C3-C74
Ref ID: 455
EXCLUDE-GUIDELINE

Salmasi, A.-M., Frost, P., & Dancy, M. 2005. Left ventricular diastolic function in normotensive subjects 2 months after acute myocardial infarction is related to glucose intolerance. American Heart Journal, 150, (1) 168-174
Ref ID: 755
EXCLUDE-UNCLEAR IF PARTICIPANTS WERE HYPERGLYCAEMIC ON ADMISSION

Santaguida, P.L., Balion, C., Hunt, D., Morrison, K., Gerstein, H., Raina, P., Booker, L., & Yazdi, H. 2005. Diagnosis, prognosis, and treatment of impaired glucose tolerance and impaired fasting glucose. Evidence Report/Technology Assessment, 128, 312 available from: http://www.ahrq.gov/clinic/tp/impglutp.htm
Ref ID: 1914
EXCLUDE-NOT SPECIFIC TO ACS

Savage, M. 2004. Screening for glucose intolerance post myocardial infarction. Diabetic Medicine, Supplement, 21, (4) 12-13
Ref ID: 850
EXCLUDE-CASE STUDY/EDITORIAL

Sen, K., Mukherjee, A.K., Dharchowdhury, L., & Chatterjee, A. 2008. A study to find out the proportion of prediabetes in patients with acute coronary syndrome in a Medical College of Kolkata. Journal of the Indian Medical Association, 106, (12) 776-778
Ref ID: 323
EXCLUDE-NOT ACCESSIBLE

Singh, R.B., Vargoa, V., Mechirova, V., & Pella, D. 2008. Acute coronary syndrome: A progression of pre-metabolic syndrome. World Heart Journal, 1, (4) 307-308
Ref ID: 251
EXCLUDE-NOT ACCESSIBLE

Stranders, I., Diamant, M., Van Gelder, R.E., Spruijt, H.J., Twisk, J.W.R., Heine, R.J., & Visser, F.C. 2004. Admission Blood Glucose Level as Risk Indicator of Death after Myocardial Infarction in Patients with and without Diabetes Mellitus. Archives of Internal Medicine, 164, (9) 982-988
Ref ID: 876
EXCLUDE-FOCUS ON RISK OF MORTALITY

Tenerz, A., Lonnberg, I., Berne, C., Nilsson, G., & Leppert, J. 2001. Myocardial infarction and prevalence of diabetes mellitus: Is increased casual blood glucose at admission a reliable criterion for the diagnosis of diabetes?

European Heart Journal, 22, (13) 1102-1110
Ref ID: 1050
EXCLUDE-FOCUS ON PREVALANCE OF DIABETES NOT RISK FACTORS FOR PROGRESSION TO DIABETES

Venskutonyte, L., Malmberg, K., Norhammar, A., & Ryden, L. 2009. Journal of Diabetes, Conference: 3rd International Congress on Prediabetes and the Metabolic Syndrome Nice France. Conference Start: 20090401 Conference End: 20090404. Conference: 3rd International Congress on Prediabetes and the Metabolic Syndrome Nice France. Conference Start: 20090401 Conference End: 20090404. Conference Publication: (var.pagings) A66
Ref ID: 255
EXCLUDE-CONFERENCE PAPER

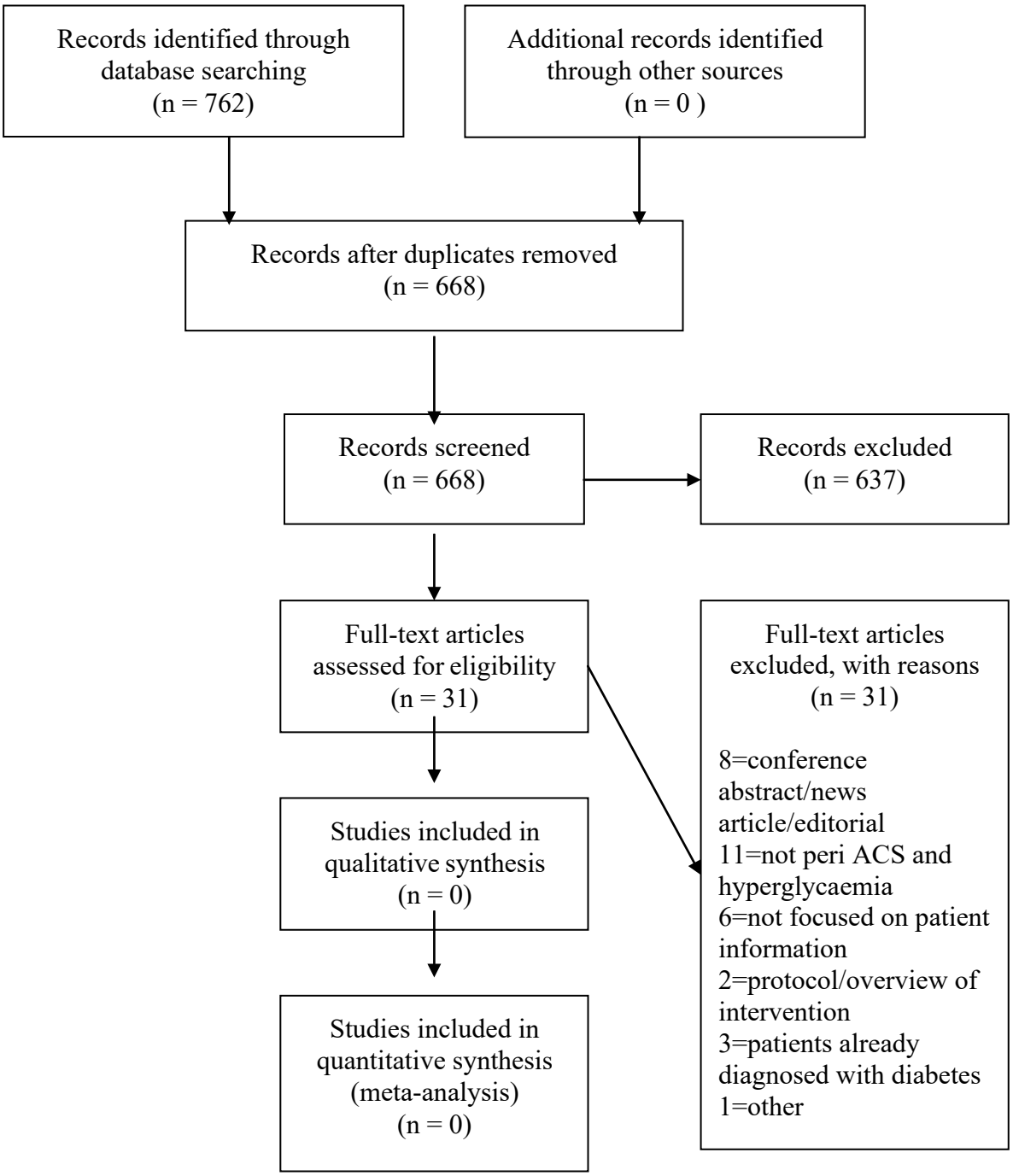
Wallander, M., Malmberg, K., Norhammar, A., Ryden, L., & Tenerz, A. 2008. Oral glucose tolerance test: a reliable tool for early detection of glucose abnormalities in patients with acute myocardial infarction in clinical practice: a report on repeated oral glucose tolerance tests from the GAMI study. Diabetes Care, 31, (1) 36-38
Ref ID: 1368
EXCLUDE-FOCUS ON RELIABILITY OF OGTT

Wannamethee, S.G. 2008. The metabolic syndrome and cardiovascular risk in the British regional heart study. International Journal of Obesity, 32, (SUPPL. 2) S25-S29
Ref ID: 403
EXCLUDE-NOT PERI ACS AND HYPERGLYCAEMIA. FOCUS ON RISK OF CHRONIC HEART DISEASE AND DIABETES IN PARTICIPANTS WITHOUT HISTORY OF THESE CONDITIONS

Zareba, W. 2008. Hyperglycemia as a risk factor in postinfarction patients. Cardiology Journal, 15, (5) 399-401
Ref ID: 365
EXCLUDE-NARRATIVE REVIEW

### *Flow diagram of excluded studies for hyperglycaemia review question 4*

The flow diagram below shows an overview of the studies that were identified, included and excluded for review question 4, which focuses on the information or support that should be provided for patients with ACS and hyperglycaemia (who are at high risk for developing diabetes) while they are waiting for a referral for diabetic investigations.



## *Excluded studies*

### List of excluded studies for review question 4 (patient information)

2005. Summaries for patients. Levels of risk factors associated with heart attacks.[Original report in Ann Intern Med. 2005 Mar 15;142(6):393-402; PMID: 15767617]. Annals of Internal Medicine, 142, (6) I23
Ref ID: 64
EXCLUDE-FOCUS ON RISK FACTORS FOR CHRONIC HEART DISEASE NOT PATIENT INFORMATION

2007. Newsline: another risk factor turns up for diabetes. Clinical Advisor for Nurse Practitioners, 10, (10) 11-12
Ref ID: 546
EXCLUDE-NEWS ARTICLE

Antman, E.M.A. 2004. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction - Executive summary: A report of the American College of cardiology/American heart association task force on practice guidelines (writing committee to revise the 1999 guidelines for the management of patients with acute myocardial infarction). Canadian Journal of Cardiology, 20, (10) 977-1025
Ref ID: 445
EXCLUDE-NOT FOCUSED ON PATIENT INFORMATION FOR HYPERGLYCAEMIA

Basina, M.K. 2002. Effectiveness of diabetes management: Is improvement feasible? American Journal of Medicine, 112, (8) 670-672
Ref ID: 492
EXCLUDE-FOCUS ON MANAGEMENT OF DIAGNOSED DIABETES

Clark, C.M., Jr. 1999. The National Diabetes Education Program: Changing the way diabetes is treated. Annals of Internal Medicine, 130, (4 I) 324-326
Ref ID: 508
EXCLUDED-OVERVIEW OF DIABETES EDUCATION PROGRAM

De Mulder, M.O. 2010. European Heart Journal, Conference: European Society of Cardiology, ESC Congress 2010 Stockholm Sweden. Conference Start: 20100828 Conference End: 20100901. Conference Publication: (var.pagings) 349
Ref ID: 266
EXCLUDE-CONFERENCE ABSTRACT

Del Prato S.Bianchi 2007. Pharmacological intervention in prediabetes: Considering the risks and benefits. Diabetes, Obesity and Metabolism, 9, (SUPPL.1) 17-22
Ref ID: 328
EXCLUDE-NOT PERI ACS AND HYPERGLYCAEMIA

Engberg, S., Vistisen, D., Lau, C., Glumer, C., Jorgensen, T., Pedersen, O., & Borch-Johnsen, K. 2009. Progression to impaired glucose regulation and diabetes in the population-based Inter99 study.[Erratum appears in Diabetes Care. 2009 Sep;32(9):1751]. Diabetes Care, 32, (4) 606-611
Ref ID: 10
EXCLUDE-NOT PERI ACS AND HYPERGLYCAEMIA

Engelgau, M. C. S. R. A. B.-J. K. N. K. Prevention of Type 2 Diabetes: Issues and Strategies for Identifying Persons for Interventions. Diabetes Technology & Therapeutics 6, 874-882. 2004.
Ref ID: 656

EXCLUDE-NOT PERI ACS AND HYPERGLYCAEMIA

Gavin III, J.R.P. 2003. Reducing Cardiovascular Disease Risk in Patients with Type 2 Diabetes: A Message from the National Diabetes Education Program. American Family Physician, 68, (8) 1569-1578
Ref ID: 470
EXCLUDE-NOT FOCUSED ON PATIENT INFO FOR POTENTIAL DIABETES

Hanna-Moussa, A., Gardner, M.J., Romayne, K.L., & Sowers, J.R. 2009. Dysglycemia/prediabetes and cardiovascular risk factors. Reviews in Cardiovascular Medicine, 10, (4) 202-208
Ref ID: 12
EXCLUDE-NOR FOCUSED ON PATIENT INFORMATION/ADVICE

Heinig, R.E. 2006. The patient with diabetes: Preventing cardiovascular complications. Clinical Cardiology, 29, (10 SUPPL.) II13-II20
Ref ID: 371
EXCLUDE-FOCUS ON PATIENTS ALREADY DIAGNOSED WITH DIABETES

Hristova, K.M. 2010. Circulation, Conference: World Congress of Cardiology Scientific Sessions 2010, WCC 2010 Beijing China. Conference Start: 20100616 Conference End: 20100619. Conference Publication: (var.pagings) e195
Ref ID: 244
EXCLUDE-CONFERENCE ABSTRACT

Jaber, L.A., Halapy, H., Fernet, M., Tummalapalli, S., & Diwakaran, H. 1996. Evaluation of a pharmaceutical care model on diabetes management. The Annals of pharmacotherapy, 30, (3) 238-243 available from: http://www.mrw.interscience.wiley.com/cochrane/clcentral/articles/791/CN-00130791/frame.html
Ref ID: 654
EXCLUDE-NOT FOCUSED ON PATIENT INFORMATION

Kane, J.S.K. 2009. Diabetes, Conference: 69th Annual Meeting of the American Diabetes Association New Orleans, LA United States. Conference Start: 20090605 Conference End: 20090609. Conference Publication: (var.pagings)
Ref ID: 164
EXCLUDE-CONFERENCE ABSTRACT

Lansdown, A.J.R. 2010. Diabetic Medicine, Conference: Diabetes UK Annual Professional Conference Liverpool United Kingdom. Conference Start:

20100303 Conference End: 20100305. Conference Publication: (var.pagings) 90
Ref ID: 155
EXCLUDE-CONFERENCE ABSTRACT

MacFarlane, I.A.W. 2007. Focus on smoking and diabetes. Practical Diabetes International, 24, (3) 117-118
Ref ID: 322
EXCLUDE-FOCUS ON LINK BETWEEN SMOKING AND DIABETES NOT PATIENT INFORMATION

Mozaffarian, D., Marfisi, R., Levantesi, G., Silletta, M.G., Tavazzi, L., Tognoni, G., Valagussa, F., & Marchioli, R. 2007. Incidence of new-onset diabetes and impaired fasting glucose in patients with recent myocardial infarction and the effect of clinical and lifestyle risk factors. Lancet, 370, (9588) 667-675
Ref ID: 28
EXCLUDE-NOT PERI ACS AND HYPERGLYCAEMIA

Murray, E., Burns, J., See, T.S., Lai, R., & Nazareth, I. 2005. Interactive Health Communication Applications for people with chronic disease. Cochrane Database of Systematic Reviews: Reviews 2005 (4) available from: http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD004274/frame.html
Ref ID: 623
EXCLUDE-NOT SPECIFIC TO PATIENTS WITH ACS AND HYPERGLYCAEMIA

Noknoy, S., Chamnan, P., & Anothaisintawee, T. 2009. Theory-based behavioural interventions for prediabetic state and people with diabetes mellitus. Cochrane Database of Systematic Reviews: Protocols 2009 (4) available from: http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD008082/frame.html
Ref ID: 613
EXCLUDE-PROTOCOL

Orozco, L.J., Buchleitner, A.M., Gimenez, P.G., Figuls, M., Richter, B., & Mauricio, D. 2008. Exercise or exercise and diet for preventing type 2 diabetes mellitus. Cochrane Database of Systematic Reviews: Reviews 2008 (3) available from: http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD003054/frame.html
Ref ID: 617
EXCLUDE-PAPERS DONT INCLUDE PATIENTS WITH ACS (HYPERGLYCAEMIA ONLY)

Rasmussen, S.S.L. 2009. Diabetologia, Conference: 45th EASD Annual Meeting of the European Association for the Study of Diabetes Vienna Austria. Conference Start: 20090930 Conference End: 20091002. Conference Publication: (var.pagings) S327
Ref ID: 180
EXCLUDE-CONFERENCE ABSTRACT

Ratner, R., Goldberg, R., Haffner, S., Marcovina, S., Orchard, T., Fowler, S., Temprosa, M., & Diabetes Prevention Program Research Group 2005. Impact of intensive lifestyle and metformin therapy on cardiovascular disease risk factors in the diabetes prevention program. Diabetes Care, 28, (4) 888-894
Ref ID: 63
EXCLUDE-NOT SPECIFIC TO PATIENTS WITH ACS AND HYPERGLYCAEMIA

Rosenstock, J. 2007. Reflecting on type 2 diabetes prevention: More questions than answers! Diabetes, Obesity and Metabolism, 9, (SUPPL.1) 3-11
Ref ID: 502
EXCLUDE-NOT PERI ACS AND HYPERGLYCAEMIA

Tenerz, A.L., I 2001. Myocardial infarction and prevalence of diabetes mellitus: Is increased casual blood glucose at admission a reliable criterion for the diagnosis of diabetes? European Heart Journal, 22, (13) 1102-1110

Ref ID: 500
EXCLUDE-NOT FOCUSED ON PATIENT INFORMATION

Tuomilehto, J. &. L. J. The major diabetes prevention trials. Current diabetes review 3, 115-122. 2003.
Ref Type: Generic
Ref ID: 655

EXCLUDE-NOT PERI ACS AND HYPERGLYCAEMIA

Unger, J. & Moriarty, C. 2008. Preventing Type 2 Diabetes. Primary Care - Clinics in Office Practice, 35, (4) 645-662
Ref ID: 362
EXCLUDE-NOT PERI ACS AND HYPERGLYCAEMIA

Uusitupa, M.I. 1996. Early lifestyle intervention in patients with non-insulin-dependent diabetes mellitus and impaired glucose tolerance. Annals of medicine, 28, (5) 445-449 available from: http://www.mrw.interscience.wiley.com/cochrane/clcentral/articles/538/CN-00134538/frame.html
Ref ID: 653
EXCLUDE-NOT PERI ACS AND HYPERGLYCAEMIA

Vancea, D.M., Vancea, J.N., Pires, M.I., Reis, M.A., Moura, R.B., & Dib, S.A. 2009. Effect of frequency of physical exercise on glycemic control and body composition in type 2 diabetic patients. Arquivos brasileiros de cardiologia, 92, (1) 23-30 available from: http://www.mrw.interscience.wiley.com/cochrane/clcentral/articles/403/CN-00721403/frame.html
Ref ID: 637
EXCLUDE-PATIENTS ALREADY DIAGNOSED WITH TYPE 2 DIABETES

Varadhan, L.W. 2009. Diabetes, Conference: 69th Annual Meeting of the American Diabetes Association New Orleans, LA United States. Conference

Start: 20090605 Conference End: 20090609. Conference Publication: (var.pagings)
Ref ID: 159
EXCLUDE-CONFERENCE ABSTRACT

Zhao, Z.Y.W. 2010. Cardiology, Conference: International Heart Forum Beijing China. Conference Start: 20100811 Conference End: 20100813. Conference Publication: (var.pagings) 44
Ref ID: 260
EXCLUDE-CONFERENCE ABSTRACT

# Appendix E Evidence tables

## *Review question 1: What is the optimal inpatient metabolic management of patients presenting with hyperglycaemia and acute coronary syndrome (ACS) who have diagnosed diabetes mellitus and hyperglycaemia*

### Evidence table 1

<table>
<tr><th>Bibliographic Reference (Ref ID)</th><th>Study type/aim</th><th>Patient characteristics</th><th>Definitions</th><th>Intervention</th><th>Comparator</th><th>Length of follow-up</th><th>Outcome measures and effect size</th><th>Source of funding</th><th>Comments</th></tr>
<tr>
<td>Malmberg et al 1995 (Ref ID: 396)</td>
<td>Multicenter RCT/To test how insulin-glucose infusion followed by multidose insulin treatment in diabetic patients</td>
<td>620 (control = 314, intervention = 306) patients with AMI and diabetes. 1240 fulfilled inclusion criteria but</td>
<td><u>Diabetes:</u> Patient has been informed of diagnosis and was on prescribed treatment (diet, tablets or insulin). <u>Newly detected</u></td>
<td><u>Insulin-glucose infusion:</u> 500 ml 5% glucose with 80 IU of soluble insulin (~1 IU/6ml). Started as soon as possible after</td>
<td><u>Control:</u> Treated according to standard coronary care unit practice and did not receive insulin unless it</td>
<td>Mean time of follow-up was 344days (range 91 to 365 days).</td>
<td>Mortality:
<table>
<tr><th>Time</th><th>Control (%)</th><th>Infusion (%)</th><th>Mortality reduction</th></tr>
<tr><td>In hospital</td><td>35 (11.1)</td><td>28 (9.1)</td><td>18% (ns)</td></tr>
<tr><td>3 months</td><td>49 (15.6)</td><td>38 (12.4)</td><td>21% (ns)</td></tr>
<tr><td>1 year</td><td>82 (26.1)</td><td>57 (18.6)</td><td>29% (p = 0.03)</td></tr>
</table>
The relative reduction in mortality was 29% by crude method and 31% with Cox model (CI 4% to 51%).</td>
<td>Swedish Heart-Lung Foundation, Karolinska Institutet and Hoechst Marion Roussel Sweden</td>
<td>DIGAMI 1 study. Patients received treatment other than glucose-insulin infusion according to predefined guidelines.</td>
</tr>
</table>

<table>
<tr><th>Bibliographic Reference (Ref ID)</th><th>Study type/aim</th><th>Patient characteristics</th><th>Definitions</th><th>Intervention</th><th>Comparator</th><th>Length of follow-up</th><th>Outcome measures and effect size</th><th>Source of funding</th><th>Comments</th></tr>
<tr>
<td></td>
<td>with Acute Myocardial Infarction (AMI) affected mortality during 12 months of follow up.</td>
<td>620 excluded. <u>Inclusion criteria:</u> suspected AMI within preceding 24 hours and previously known diabetes and blood glucose > 11mmol/l or blood glucose > 11mmol/l without diabetes. <u>Stratification:</u> based on risk and previous use of insulin. High risk patients fulfilled ≥</td>
<td><u>diabetes</u>: Admission blood glucose ≥ 11 mmol/litre. <u>AMI:</u> ≥ 2 of following criteria fulfilled; 1) chest pain for ≥ 15 mins; 2) ≥ 2 values of serum creatine kinase (S-CK) and S-CK isoenzyme B (S-CKB) or serum lactic dehydrogenase (S-LD) above the normal range (normal</td>
<td>arrival. Infusion was continued until stable normoglycaemia was attained for ≥ 24 hours. <u>Subcutaneous insulin:</u> administration of soluble insulin using insulin pen 3 times daily before meals combined with medium long acting insulin in the evening.</td>
<td>was deemed clinically indicated.</td>
<td></td>
<td>
<table>
<tr><td></td><td colspan="4">Strata*</td></tr>
<tr><td>Time</td><td>1</td><td>2</td><td>3</td><td>4</td></tr>
<tr><td>Control 3m</td><td>18 (13.5)</td><td>10 (15.2)</td><td>8 (12.3)</td><td>13 (26.0)</td></tr>
<tr><td>Control 1yr</td><td>24 (18.0)</td><td>21 (31.8)</td><td>14 (21.5)</td><td>23 (46.0)</td></tr>
<tr><td>Insulin 3m</td><td>9 (6.5)</td><td>11 (17.5)</td><td>7 (13.0)</td><td>11 (22.0)</td></tr>
<tr><td>Insulin 1yr</td><td>12 (8.6)</td><td>17 (27)</td><td>10 (18.5)</td><td>18 (36.0)</td></tr>
<tr><td>Mortality reduction (3m)</td><td>52%**</td><td>-11%</td><td>0%</td><td>15%</td></tr>
<tr><td>Mortality reduction (1yr)</td><td>52%**</td><td>15%</td><td>14%</td><td>22%</td></tr>
</table>
* As defined in patient characteristics, **p = 0.046, p = 0.02 log rank test<br>
In stratum 1 the mortality reduction was 52% after 3 months (p = 0.046) and this difference persisted at one year
</td>
<td></td>
<td>Possible AMI defined in 3% of infusion group and 7% in control. Fasting blood glucose also available for 3 month follow-up but not reported in table. Authors note that revascularisation procedures did not differ between groups. There</td>
</tr>
</table>

| Bibliographic Reference (Ref ID) | Study type/aim | Patient characteristics | Definitions | Intervention | Comparator | Length of follow-up | Outcome measures and effect size | Source of funding | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | 2 of following criteria; age > 70 years, history of previous AMI and/or congestive heart failure (CHF) or ongoing treatment with digitalis. Pre defined strata; 1) no insulin & low risk, 2) no insulin & high risk, 3) insulin & low risk and 4) insulin & high risk. | +2SD), including an LD-isoenzyme pattern typical of myocardial damage; and 3) development of new Q waves in ≥ 2 standard ECG leads. **Possible AMI:** typical chest pain with only 1 S-CK or S-LD value above normal range and/or new Q waves in one ECG only. **Reinfarction:** new AMI | This was started immediately after cessation of infusion, according to regime, with aim of achieving normoglycaemia. Subcutaneous insulin was given 4 times daily for ≥ 3 months. | | | with mortality rate of 8.6% in infusion group and 18.0% in control (relative risk reduction 52%, p = 0.02).<br>**Morbidity:**<br>During the hospital period the control group did not significantly differ from the infusion group regarding reinfarction (4% vs. 5%), ventricular fibrillation (5% vs. 3%), high degree atrioventricular conduction disturbances (3% vs. 7%) or CHF (48% vs. 50%). There was a significant difference between hospital stay (11.3 ± 13.3 days in infusion group vs. 9.5 ± 9.4 days in control, p = 0.04).<br>**Measures of blood glucose and adverse events:**<br>Significantly higher numbers of patients experienced hypoglycaemia in the infusion group compared to control during the first 24 hours (46 vs. 0, p < 0.0001). | | were no sub group analyses for those who had reperfusion and those who didn't and those who were suffering from heart failure and those who weren't. |

<table>
<tr><th>Bibliographic Reference (Ref ID)</th><th>Study type/aim</th><th>Patient characteristics</th><th>Definitions</th><th>Intervention</th><th>Comparator</th><th>Length of follow-up</th><th>Outcome measures and effect size</th><th>Source of funding</th><th>Comments</th></tr>
<tr><td></td><td></td><td><u>Baseline characteristics</u>: 62% male & 38% female. Mean age for control = 68 ± 9 and for infusion = 67 ± 9. Mean blood glucose shown in outcome measures. Diabetes status: non insulin (control = 265 84%, infusion = 251 82%), insulin dependent (control = 49 16%,</td><td>> 72 hours after index infarct.</td><td></td><td></td><td></td><td>
<table>
<tr><td>Blood glucose (mmol/litre)</td><td>Control</td><td>Infusion</td><td>p-value</td></tr>
<tr><td>At randomisation</td><td>15.7±4.2</td><td>15.4±4.1</td><td>NS</td></tr>
<tr><td>24 hrs after randomisation</td><td>11.7±4.1</td><td>9.6±3.3</td><td>< 0.0001</td></tr>
<tr><td>At discharge</td><td>9.0±3.0</td><td>8.2±3.1</td><td>< 0.01</td></tr>
</table>
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<tr><td></td><td></td><td>infusion = 55 18%) and previously unknown diabetes (control = 47 15%, infusion = 31 10%). The groups were well matched in terms of baseline characteristics.</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Malmberg et al 1996 (Ref ID: 378)</td><td>Analysis of DIGAMI 1 to report the influence of insulin therapy on early and long-term</td><td>For details please see above DIGAMI 1 study. Groups were well balanced for patient characteristics. 50%</td><td>See above for DIGAMI 1 study. <u>Ventricular tachyarrhythmias</u>: The presence of either ventricular premature</td><td>See above for details of DIGAMI 1 study. Insulin group received insulin-glucose infusion followed by</td><td><u>Control:</u> Treated according to standard coronary care unit practice and did not receive</td><td></td><td><u>Mortality:</u><table><tr><td>Mortality</td><td>Total (%)</td><td>Control (%)</td><td>Infusion (%)</td><td>P-value</td></tr><tr><td>Hospital</td><td>63 (10)</td><td>35 (11)</td><td>28 (9)</td><td>ns</td></tr><tr><td>Discharge (12 months)</td><td>77 (13)</td><td>47 (15)</td><td>30 (10)</td><td>< 0.05</td></tr><tr><td>Total</td><td>140 (23)</td><td>82 (26)</td><td>58 (19)</td><td>< 0.05</td></tr></table>After one year the total mortality had</td><td>Swedish Heart-Lung Foundation, Karolinska Institutet and Hoechst Marion Roussel</td><td>The authors concluded that insulin-glucose infusion followed by subcutaneous insulin treatment</td></tr>
</table>

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| | cause-specific mortality and morbidity, with special reference to fatal and non-fatal reinfarction | were thrombolysed, 54% received intravenous nitro-glycerine & 17% were fully heparinised during the acute period in hospital. | beats or ventricular tachycardia requiring antiarrhythmic treatment, or documented ventricular fibrillation (VF) was included. VF defined as early if within 48 hrs of symptom onset and late if after. **Atrioventricular block**: Only high grade AV-blocks (II-III) were considered. The | multidose subcutaneous insulin treatment for at least 3 months. | insulin unless it was deemed clinically indicated. | | decreased by 30% in the infusion group (p = 0.027).<br>During 1 year follow-up the specific causes of death included HF, sudden death, myocardial rupture, stroke, non classified and non cardiovascular. Most died of CHF (66%). There was a trend towards less cardiovascular deaths of all kinds, and specifically for sudden death, in the infusion group compared to controls but these were non-significant.<br>Among strata 1 patients, mortality had significantly reduced during the hospital phase and this was maintained throughout follow-up (in hospital p < 0.05, 3-month p < 0.05 and 1 year p = 0.020).<br>**Morbidity:**<br>During hospitalisation the control group did not differ from the infusion group regarding the incidence of reinfarction (4% vs. 5%), ventricular fibrillations (5% vs. 3%), high degree atrioventricular conduction disturbances (3% vs. 7%) or CHF (48% vs. 50%). During 1 year follow-up 108 (18%) patients suffered reinfarction (55 in control vs. 53 in infusion group, ns). | Sweden | in patients with diabetes and AMI favourably influences 1 year mortality by reducing all cardiovascular causes of death. This therapeutic regimen seems to have particular impact on fatal reinfarctions. |

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| | | | conduction defect had to be treated to be noted in case record.<br>**CHF:** clinical and/or radiological signs of pulmonary congestion resulting in the institution of treatment. | | | | After 1 year there were 25 fatal reinfarctions in control compared to 15 in infusion group. This corresponds to reduction of 40% (CI -15% to 68%, p = 0.12). In all, 45% of reinfarctions were fatal in control group compared to 28% in infusion group (ns).<br>**Measures of blood glucose and adverse events:**<br>Fasting blood glucose after 1 year did not differ between groups. After 1 year 3 patients in control group and 8 in infusion group had hypoglycaemia but this difference was not significant. | | |
| Malmberg et al 1997 (Ref ID: 367) | Analysis of DIGAMI 1 for long-term survival | For details please see above DIGAMI 1 study. The 2 groups were well balanced at the time of randomisat | For details please see above DIGAMI 1 study. | For details please see above DIGAMI 1 study. | For details please see above DIGAMI 1 study. | The mean (range) follow-up was 3.4 years (1.6-5.6 years) and no patients were lost | **Hospital and 1 year mortality:**<br>During the initial year of follow-up, including deaths in hospital, 82 (26%) patients died in the control group compared with 58 (19%) in the insulin group. This corresponds to a relative reduction in mortality of 30% (p = 0.027). Most of the reduction occurred after hospital discharge. Only in patients without previous insulin treatment and at low cardiovascular | Swedish Heart-Lung Foundation, Karolinska Institutet and Hoechst Marion Roussel | The authors concluded that insulin-glucose infusion followed by intensive subcutaneous insulin |

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<tr><td></td><td></td><td>ion.</td><td></td><td></td><td></td><td>to follow-up as regards mortality.</td><td>risk (strata 1, 44% of all patients) was this reduction already significant during the hospital phase (from 12% in control group to 5% in the insulin group, relative reduction = 58%, p < 0.05). Absolute reduction in risk was 11%, relative risk 0.72 (CI 0.55-0.92), p = 0.011).<br><u>Long-term mortality:</u><br>During continued follow-up there were 138 (44%) deaths in the control group compared with 102 (33%) in the infusion group. The relative reduction in mortality at the end of follow-up was 28% by the Cox model (CI 8% to 45%, p = 0.011)<br><u>Long-term mortality by strata:</u>
<table>
<tr><td></td><td colspan="4">Strata*</td></tr>
<tr><td>Detail</td><td>1 (n = 272)</td><td>2 (n = 129)</td><td>3 (n = 119)</td><td>4 (n = 100)</td></tr>
<tr><td>Mean follow up (yrs)</td><td>3.4</td><td>3.3</td><td>3.4</td><td>3.5</td></tr>
<tr><td>Total mortality</td><td>69</td><td>69</td><td>42</td><td>60</td></tr>
<tr><td colspan="5">Mortality by group</td></tr>
<tr><td>Control</td><td>44</td><td>35</td><td>26</td><td>33</td></tr>
</table></td><td>Sweden</td><td>treatment in diabetic patients with AMI improves long-term survival by nearly a third and the effect seems to last for at least 3.5 years. One limitation is that exact information about insulin treatment during long-term follow-up is not available.</td></tr>
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| | | | | | | | <table><tr><td></td><td>(33)</td><td>(53)</td><td>(40)</td><td>(66)</td></tr><tr><td>Insulin</td><td>25 (18)</td><td>34 (54)</td><td>16 (30)</td><td>27 (54)</td></tr><tr><td>P-value</td><td>0.004</td><td>> 0.2</td><td>> 0.2</td><td>> 0.2</td></tr></table> As defined in patient characteristics in DIGAMI 1 above.<br>The most apparent effect was achieved in strata 1, with an absolute reduction in mortality of 15%, from 33% in control to 18% in insulin group. This corresponds to a relative reduction of 51% (19% to 70%, p = 0.004) by Cox model | | |

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| Malmberg et al 1997 (Ref ID: 2181) | The present report describes the short and long-term prognostic factors in diabetic patients with AMI by applying multivariate statistics on the DIGAMI cohort. | For details please see above DIGAMI 1 study. 38% were female and 62% were male. The female group was older than the male (70 ± 9 vs. 66 ± 9 years; p < 0.001) and had fewer previous infarctions (28 vs. 44%, p < 0.001). Hypertension was more prevalent among women | For details please see above DIGAMI 1 study | For details please see above DIGAMI 1 study | For details please see above DIGAMI 1 study | All patients were followed prospectively for 1 year with scheduled visits at 3 months and 12 months after randomisation. No patient was lost to follow-up. | **Mortality:**<br>The overall 1 year mortality tended to be higher among females than males (26.3 vs. 20.4%, p = 0.092)<br>**Univariate prediction of mortality**:<br>In the entire patient group age, previous CHF, previous MI, previous angina pectoris, previous treatment with digitalis or insulin and the duration of diabetes were associated with mortality after 1 year. Patients who were smokers had a significantly better prognosis at 1 year than non-smokers. In the entire patient group the most powerful predictors for an unfavourable outcome were high blood glucose at admission (RR 1.08, CI 1.04-1.12, p = 0.0001) and new onset heart failure during hospitalisation (RR 2.87, CI 1.99-4.13, p = 0.0001). Thrombolytic therapy during the hospital phase (RR 0.60, CI 0.43-0.85, p = 0.004) and beta-blocker at discharge (RR 0.45, CI 0.31-0.66, p = 0.0001) were associated with survival.<br>**Multivariate prediction of mortality:**<br>Independent effects of concomitant treatment on 1 year mortality (following correction for age, gender and | Swedish Heart-Lung Foundation, Karolinska Institutet and Hoechst Marion Roussel Sweden | Specific RRs for the univariate predictors of mortality are not presented in the evidence table. The authors concluded that good metabolic control and not conventional risk factors is of major importance for diabetic patients sustaining AMI. Also treatment with beta blockade |

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| | | than men (56 vs. 44%, p < 0.01) and the duration of diabetes was longer in the female group (11 ± 11 vs. 9 ± 9 years, p < 0.05). With these exceptions there were no sex differences regarding baseline characteristic. | | | | | intensive insulin by multivariate Cox regression) showed that among all patients; thrombolysis (RR 0.61, CI 0.41-0.92, p = 0.018) and treatment with beta blockers at hospital discharge (RR 0.53, CI 0.36-0.78, p = 0.001) besides intensive insulin treatment (RR 0.65, CI 0.44-0.96, p = 0.0327) independently reduced 1 year mortality. Independent effects of baseline characteristics on 1 year mortality showed that in the entire patient group age (RR 1.07, CI 1.04-1.10, p = 0.0001), previous CHF (RR 2.10, CI 1.37-3.21, p = 0.0007) and previous insulin treatment (RR 1.58, CI 1.05-2.39, p = 0.028) were independent predictors for fatal outcome during the first year of follow-up. It was also found that elevated $HbA_{1c}$ (p < 0.0001), tachycardia (p < 0.0001), presence of pulmonary rales at admission (p < 0.01) and a high body weight (p < 0.01) were all independently linked to hyperglycaemia at admission in multivariate analysis. | | seems to be of special importance in this category of patients. |
| Malmberg et al 1999 | Analysis of DIGAMI 1 | For details please see above | For details please see above | For details please see above | For details please | The mean time of | **Mortality:**<br>During long-term follow-up there were 240 deaths (39%), 138 in control group | Swedish Heart-Lung | The authors concluded |

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| (Ref ID: 207a) | to describe factors influencing the long-term prognosis and effects of concomitant treatment by applying univariate and multivariate statistical analyses. | DIGAMI 1 study. The 2 groups were well balanced at the time of randomisation. | DIGAMI 1 study. **Type of diabetes:** dependent on clinical history. **Non-insulin dependent diabetes (NIDDM):** > 40 years at diagnosis and did not need insulin for ≥ 2 years after diagnosis and not prone to ketoacidosis. | DIGAMI 1 study. | see above DIGAMI 1 study. **Control group:** received conventional treatment at the discretion of the physician in charge. | follow-up was 3.4 years (range 1.6 to 5.6 years) and did not differ between patients within the 4 strata. | (mortality 44%) and 102 in infusion group (mortality 33%, p = 0.011). This corresponds to a relative mortality reduction (at the end of follow-up) of 28% (CI 8% to 45%) using Cox model. Patients in strata 1 had an absolute mortality reduction of 15%, from 44 deaths (33%) in control group to 25 deaths (18%) in infusion group. This corresponds to a relative reduction of 51% (CI 19% to 70%, p = 0.004). **Univariate prediction:** In the control group the following factors were found to be significantly associated with long-term mortality; age RR = 1.07 (1.04-1.10, p < 0.001), male sex RR = 0.70 (0.50-0.98, p < 0.05), previous MI RR = 1.42 (1.01-1.99, p < 0.05), previous CHF RR = 2.37 (1.67-3.38, p < 0.001), previous hypertension RR = 1.45 (1.04-2.03, p < 0.05), smoking RR = 0.58 (0.37-0.92, p < 0.05), blood glucose at admission RR = 1.09 (1.05-1.13, p < 0.001), $HbA_{1c}$ RR = 1.13 (1.04-1.25, p < 0.01), CHF during hospitalisation RR = 2.59 (1.82-3.68, p < 0.001), thrombolysis RR = 0.69 (0.49-0.97, p < 0.05) and beta blockers at discharge RR = 0.45 (0.31- | Foundation, Karolinska Institutet and Hoechst Marion Roussel Sweden | that mortality is predicted by age, previous HF and the severity of the gluco-metabolic state at admission. Institution of intensive insulin reduces this risk considerably. Beta blockers also have striking preventative effect in diabetics with MI. Those prescribed ACE may |

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| | | | | | | | 0.65, p < 0.001).<br>In the infusion group the following factors were found to be significantly associated with long-term mortality; age RR = 1.07 (1.05-1.10, p < 0.001), previous MI RR = 2.01 (1.36-2.97, p < 0.001), previous CHF RR = 2.90 (1.95-4.30, p < 0.001), diabetes duration RR = 1.02 (1.01-1.04, p < 0.01), blood glucose at admission RR = 1.05 (1.01-1.11, p < 0.05), CHF during hospitalisation RR = 2.40 (1.59-3.62, p < 0.001) and thrombolysis RR = 0.44 (0.29-0.67, p < 0.001).<br>**Multivariate prediction:** In the control group the following factors were found to be significantly associated with long-term mortality using Cox regression; age RR = 1.09 (1.06-1.12, p < 0.001), previous CHF RR = 2.37 (1.50-3.74, p < 0.001), admission blood glucose + 1mmol/litre RR = 1.06 (1.01-1.11, p < 0.05) and $HbA_{1c}$ on admission RR = 1.15 (1.03-1.29, p < 0.05).<br>In the infusion group the following factors were found to be significantly associated with long-term mortality; age RR = 1.08 (1.05-1.12, p < 0.001), previous history of CHF RR = 2.28 | | have more severe CHF |

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| | | | | | | | (1.33-3.73, p < 0.01) and diabetes duration (1 added yr) RR = 1.03 (1.01-1.05, p < 0.01).<br>**Effects of treatment:**<br>Independent effects of concomitant treatment on long-term mortality after correction for age, sex and CHF during the hospital period found thrombolysis RR = 0.63 (1.43-0.92, p < 0.05), beta-blockade at discharge RR = 0.55 (0.38-0.79, p < 0.01) and ACE inhibitor at discharge RR = 1.50 (1.04-2.30, p < 0.05) were significant predictors in the control group. Only thrombolysis RR = 0.44 (0.28-0.72, p < 0.001) was a significant predictor in the infusion group. Overall, intensive insulin RR = 0.67 (0.51-0.88, p < 0.01) was also associated with long-term mortality. | | |

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| Malmberg 2004 (Ref ID: 144a) | Analysis of DIGAMI 1 for findings regarding effects on mortality and morbidity. | For details please see above DIGAMI 1 study. The 2 groups were well balanced at the time of randomisation | For details please see above DIGAMI 1 study. **Hypoglycaemia:** blood glucose level < 3 mmol/litre with or without symptoms. | For details please see above DIGAMI 1 study. | For details please see above DIGAMI 1 study. | For details please see above DIGAMI 1 study. | **Mortality:** Overall, the intensive approach reduced the long-term relative mortality (at 3.4 years of follow-up) by 25% in the insulin treated group (p = 0.011). This corresponds to an absolute mortality reduction of 11%. **Mortality of strata 1:** At dismissal patients in strata 1 had a 58% reduction in mortality (p < 0.05). This benefit was sustained throughout follow-up with a 50% reduction at 12 months. At longer term follow-up (3.4 years) there was a highly significant 45% reduction in mortality (33% vs. 18%, p = 0.004). | | The author acknowledges that as patients were given both immediate infusion and long-term metabolic control, it is impossible to determine which part contributes most to the favourable outcome or whether both elements were important. |
| Malmberg et al 2005 | DIGAMI 2-multicentr | 1253 patients were | **Hyperglycaemia:** patients | **Group 1:** Insulin-glucose | **Group 3:** the glucose | All patients were | **Mortality (intention to treat):** Overall there were 277 deaths (21.3%) and mortality did not significantly differ | The Swedish Heart- | Concomitant therapy was used |

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| (Ref ID: X) | e, prospective, randomised open trial comparing three different management strategies in patients with type 2 diabetes and AMI. | allocated to 3 groups (group 1 = 474, group 2 = 473, and group 3 = 306). At discharge 84, 84 and 84% of patients in groups 1, 2 and 3 fulfilled the diagnosis of MI- almost all remaining patients had coronary artery disease. **Inclusion criteria:** patients with | with established type 2 diabetes or an admission blood glucose > 11.0mmol/litre were eligible for inclusion. **MI:** diagnosed according to joint recommendation of ESC and ACC. **Reinfarction:** new event > 72 hours from index infarction. **Stroke:** unequivocal signs of | infusion 500 ml 5% glucose with 80 IU of soluble insulin (~1 IU/6ml) was given with the objective to decrease blood glucose as fast as possible and keep it within 7 and 10mmol/litre. The infusion lasted until stable normoglycaemia and at least for 24 hours. Subcutaneous insulin | lowering treatment was at the discretion of the responsible physician and according to local routines. Target values were not defined in this group. | followed up for a minimum of 6 months and the maximum time of follow-up was 3 years. No patients were lost to follow-up. | between the 3 groups. After 2 years of follow-up, the Kaplan-Meier estimated mortality was 23.4% among patients in group 1 when compared with 21.2% in group 2 (HR = 1.03, CI = 0.79-1.34, p = 0.832). The corresponding proportion in group 3 was 17.9% (group 1 vs. 3 HR = 1.26, CI = 0.92-1.72, p = 0.157). Adjusted HR for difference in previous diseases between groups 1 and 3 was 1.19 (CI 0.86-1.64, p = 0.29). Comparing groups 2 and 3, the HR = 1.23 (CI 0.89-1.69, p < 0.203). Cardiovascular causes of death were most common without any significant differences among the groups, whereas a lower incidence of non-cardiovascular deaths in group 3 explained the trend towards a somewhat lower overall mortality in this group compared with groups 2 and 3 (group 1 vs. 3, p = 0.021). There was a slight difference in mortality from malignancies, with a higher incidence in group 1 (n = 16) compared with group 2 (n = 5) and group 3 (n = 2, group 1 vs. 2, p = 0.016, group 1 vs. 3, p = 0.011). **Multivariate predictors of mortality:** | Lung Foundation, AFA Insurance, The King Gustav V and Queen Victoria Foundation, The Swedish Medical Research Council, The Swedish Diabetes Association and unconditional research grants from Aventis Sweden and Novo Nordisk Denmark. | based on evidence based international guidelines for AMI. 14% of group 3 were administered insulin-glucose infusion. During follow-up, multidose insulin was used in < 50% of patients in group 1& in between 15 and 20% in groups 2 & 3 whereas ~10% in group 1 |

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| | | established type 2 diabetes or an admission blood glucose > 11.0mmol/l admitted to coronary care units. **Baseline characteristics:** baseline characteristic, biochemical and clinical data were well balanced in most respects. However, there were significantly fewer | focal or global neurological deficit of sudden onset and a duration of > 24 hours that were judged to be of vascular origin. **Sudden cardiovascular deaths**: those that occurred within 24 hours following onset of symptoms and without any obvious reason for the fatal outcome. | was initiated at the cessation of infusion. Insulin was given as short-acting insulin before meals and intermediate long-acting insulin in the evening. The treatment goal in group 1 was a fasting blood glucose level of 5-7 mmol/litre and a non- | | | Updated blood glucose during the time of follow up (HR = 1.20 for 3mmol/litre, p < 0.001) was a significant and independent predictor together with increasing age (HR = 2.14 for 10 years, p < 0.001), previous HF (HR = 1.71, p < 0.001) and elevated serum creatinin (HR = 1.13 for 40µmol/litre, p < 0.001).<br>**Morbidity:**<br>There was a trend towards fewer secondary events in groups 2 and 3 compared to group 1. However, this difference did not reach statistical significance for stroke or myocardial reinfarction. The combined total event rate was high in the magnitude of 35-40% but did not significantly differ between the 3 groups.<br>**Glucose lowering treatment and adverse events:**<br>Blood glucose with or without symptoms < 3mmol/litre (hypoglycaemia) was more frequent during the initial 24 hours in group 1 (12.7%, symptomatic 27%) and 2 (9.6%, symptomatic 39%) than in group 3 (1.0%, symptomatic 33%). Apart from slightly but statistically significant lower blood glucose after 24 hours in groups | | and ~15-20% of those in groups 2 and 3 did not receive any glucose lowering drugs. Authors concluded that DIGAMI 2 did not support the use of acute, long-term insulin treatment to improve survival in patients with type 2 diabetes and AMI when compared |

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| | | previous MIs and a trend towards less hypertension and HF in group 3. Mean age (group 1 = 68.1, group 2 = 68.6, and group 3 = 68.4). 67% were male. Blood glucose at randomisation (1 = 12.8, 2 = 12.5, 3 = 12.9, p = 0.414). | **Hypoglycaemia:** blood glucose level < 3 mmol/litre with or without symptoms. | fasting level of < 10mmol/litre. **Group 2:** initial insulin-glucose infusion was given as above and glucose lowering treatments at the discretion of the responsible physician and according to local routines. Target values were not defined in this group. | | | 1 and 2 compared with group 3 (1 = 9.1, 2 = 9.1, 3 = 10.0, p = 0.0001), blood glucose and $HbA_{1c}$ did not differ significantly among any of the 3 groups when comparing the area under the curve of blood glucose over time. The absolute difference between these groups and group 3 was only 0.9mmol/l. The levels did not reach the targeted level between 5 and 7mmol/litre in group 1. | | with conventional management at similar levels of glucose control. However, glucose level was found to be a strong, independent predictor of long-term mortality suggesting that glucose control is still an important factor. |

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<tr><td>Mellbin et al 2009 (Ref ID: 3363)</td><td>Analysis of DIGAMI 2 to explore whether hypoglycaemic episodes during hospitalisation had an impact on total mortality and the rate of non-fatal re-infarctions and stroke during follow-up.</td><td>See DIGAMI 2 above for details. 1253 patients randomised to 3 groups. Patients experiencing hypoglycaemia were older, had a lower body weight and body mass index and more often presented with a history of HF. Moreover they were less</td><td>See DIGAMI 2 above for details. <u>Updated hypoglycaemia:</u> relates to when the hypoglycaemic event occurred, during 0-24 hours, 24-48 hrs or 48hrs-9 days.</td><td>See DIGAMI 2 above for details. <u>Group 1:</u> 24 hour insulin-glucose infusion followed by subcutaneous insulin based long-term glucose control (n = 474). <u>Group 2:</u> Same initial treatment as group 1 followed by standard glucose control (n = 473).</td><td>See DIGAMI 2 above for details. <u>Group 3:</u> Glucose lowering treatment according to local practice (n = 306)</td><td>Patients were followed up during a median of 2.1 years (interquartile range 1.03-3.00 yrs).</td><td>Mortality & morbidity:<table><tr><th>Endpoint</th><th>Patients with Hypoglycaemia (n = 153)</th><th>Patients with symptomatic hypoglycaemia (n = 45)</th></tr><tr><td>Death</td><td>39 (25.5%)</td><td>16 (35.6%)</td></tr><tr><td>Cardiovascular death</td><td>35 (22.9%)</td><td>14 (31.1%)</td></tr><tr><td>Stroke</td><td>7 (4.6%)</td><td>3 (6.7%)</td></tr><tr><td>Re-infarction</td><td>19 (12.4%)</td><td>4 (8.9%)</td></tr></table>Besides a somewhat higher total (unadjusted HR = 1.99, CI 1.20-3.29, p = 0.0076) and cardiovascular mortality (unadjusted HR = 2.06, CI 1.20-3.53, p = 0.0009) among patients with symptomatic hypoglycaemia the event rate showed a similar pattern in those with and without hypoglycaemic episodes. However this mortality difference disappeared following adjustment for confounders (p > 0.05). <u>Predictors of subsequent</u></td><td>The Swedish Heart-Lung Foundation, AFA Insurance and unconditional research grants from Aventis Sweden and Novo Nordisk Denmark.</td><td>Further regression analyses among patients receiving glucose-insulin infusion testing an even lower cut off level 2.7 mmol/litre for hypoglycaemia did not change these results. The authors concluded that hypoglycaemia during the initial</td></tr>
</table>

| Bibliographic Reference (Ref ID) | Study type/aim | Patient characteristics | Definitions | Intervention | Comparator | Length of follow-up | Outcome measures and effect size | Source of funding | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | treated with lipid lowering drugs but more often with diuretics. $HbA_{1c}$, admission blood glucose and glucose lowering treatment at admission did not differ. The duration of diabetes was longer among patients with than those without hypoglycaemic | | | | | **<u>hypoglycaemic events:</u>**<br>Hypoglycaemia was experienced by 153 (12%) patients out of whom 45 (29%) were symptomatic. Most episodes in insulin treated patients occurred during the first 24 hours (n = 111, 12%, symptomatic n = 26, 23%). The corresponding numbers in patients on routine treatment were three (1.0%) and one, respectively.<br>Bodyweight (+1kg; OR 0.97, CI0.95-0.98, p < 0.0001) and diabetes duration (+1 year; OR 1.03, CI 1.01-1.05, p = 0.0085) remained independent predictors for subsequent hypoglycaemic events following a step-wise logistic regression. | | hospitalisation was not an independent risk factor for future morbidity or mortality in patients with type 2 diabetes and MI. Such episodes were however, more prevalent in patients at high risk for other reasons. |

| Bibliographic Reference (Ref ID) | Study type/aim | Patient characteristics | Definitions | Intervention | Comparator | Length of follow-up | Outcome measures and effect size | Source of funding | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | episodes | | | | | | | |
| Cheung et al 2006 (Ref ID: 103a) | The HI-5 study was a multicenter open-label randomised controlled trial aimed to determine whether tight glycaemic control improves outcomes for hyperglycaemic patients with AMI | 240 patients (126 in infusion therapy group and 114 in conventional therapy group). **Inclusion criteria:** 1) evidence of AMI within last 24 hours and 2) known diabetes or not diabetic with an admission blood glucose level ≥ 7.8mmol/litre | **Hypoglycaemia:** finger prick blood glucose < 3.5mmol/l, irrespective of the occurrence of symptoms. **Reinfarction:** new AMI occurring > 72 hours following index infarct. Cardiac failure: dyspnoea with radiographic evidence of pulmonary or interstitial | **Infusion Therapy Group (ITG):** patients placed on insulin at 2 units/h and 5% dextrose at 80ml/h. Insulin was titrated to maintain blood glucose between 4 and 10mmol/litre for at least 24 hours. For patients with cardiac failure, 10% dextrose | **Conventional Therapy Group (CTG):** remained on their usual diabetes therapy but metformin was temporarily discontinued. Supplemental subcutaneous short-acting insulin was permitted if blood glucose | Patients were contacted to obtain information regarding the occurrence of cardiovascular events following discharge. Outcomes were measured during the index hospital admission and after 3 and 6 months. There | **Mortality and morbidity:** There was no difference in mortality between the groups at the inpatient stage (ITG = 4.8%, CTG = 3.5%, p = 0.75), 3 months (ITG = 7.1%, CTG = 4.4%, p = 0.42) or 6 months (ITG = 7.9%, CTG = 6.1%, p = 0.62). There was lower incidence of cardiac failure during the inpatient period (12.7 vs. 22.8%, p = 0.04) and of reinfarction within 3 months (2.4 vs. 6.1%, p = 0.05) in the ITG group. There were no other differences in any of the secondary cardiac outcomes or in the occurrence of composite end points. **Sub-group analysis by diabetes status:** Among patients with diabetes there was a lower reinfarction rate in the ITG (0 vs.7.7%, p = 0.04) and a lower occurrence of composite end points (21.9 vs. 40.4%, p = 0.03) at 3 months. There were no differences in other outcome variables. Among those without diabetes, there was an incidence of cardiac failure in the ITG during the inpatient period (11.3 vs. 27.4%, p = 0.02). There were no | National Health and Medical Research Council of Australia Project Grant and Novo Nordisk Pharmaceuticals | Data for glycaemic control in the first 24 hours were collected for 97.5% of patients. The mean 24 hr blood glucose was distributed around a median level of 8.1mmol/l so the cohort was divided into ≤ 8 mmol/l and ≥ 8.1mmol/l. The authors concluded that insulin |

<table>
<tr><th>Bibliographic Reference (Ref ID)</th><th>Study type/aim</th><th>Patient characteristics</th><th>Definitions</th><th>Intervention</th><th>Comparator</th><th>Length of follow-up</th><th>Outcome measures and effect size</th><th>Source of funding</th><th>Comments</th></tr>
<tr>
<td></td>
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<td>(140mg/dl). <u>Baseline characteristics:</u> There were no differences in baseline characteristics. There was no difference between patients given PTCA (infusion = 32%, control = 39%), thrombolysis (32% vs. 32%) or no reperfusion (37% vs. 29%). The mean age was 63 ± 11 years</td>
<td>edema. <u>Cardiogenic shock:</u> cardiac failure with a systolic blood pressure < 80mmHg. <u>Composite end point:</u> death or any major cardiac event. <u>Evidence of AMI:</u> troponin-T > 0.1 µg/l or electrographic criteria of ST elevation in two limb leads.</td>
<td>was administered at 40 ml/h. All diabetes medications were discontinued temporarily. Upon cessation of infusion, patients resumed their usual diabetes medication.</td>
<td>was > 16mmol/l.</td>
<td>was no information relating to mean follow-up period but it was reported that follow-up at 6 months was successful for 94% of subjects.</td>
<td>differences in other outcome variables<br><u>Sub-group analysis by 24 hr glycaemic control</u>:<br>The mean 24 hour blood glucose was associated with risk of death in hospital (p = 0.03) and borderline at 6 months (p = 0.06).
<table>
<tr><th></th><th>24 hr mean blood glucose ≤ 8 mmol/l</th><th>24 hr mean blood glucose ≥ 8.1 mmol/l</th><th>Adjusted OR (CI)*</th><th>P-value</th></tr>
<tr><td>Inpatient mortality</td><td>0%</td><td>7%</td><td>7.2 (0.9-58.9)</td><td>0.07</td></tr>
<tr><td>3-month mortality</td><td>2%</td><td>9%</td><td>4.7 (1.0-22.4)</td><td>0.05</td></tr>
<tr><td>6-month</td><td>2%</td><td>11%</td><td>5.6 (1.2-26.1)</td><td>0.03</td></tr>
</table>
</td>
<td></td>
<td>infusion did not reduce short-term mortality following AMI using an intention to treat analysis. The mean duration of symptom onset to commencement of insulin was 13 hrs and this may have been too late for significant myocardial salvage. The authors concluded that a</td>
</tr>
</table>

| Bibliographic Reference (Ref ID) | Study type/aim | Patient characteristics | Definitions | Intervention | Comparator | Length of follow-up | Outcome measures and effect size | Source of funding | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | and 116 (48%) participants had known diabetes (all type 2). 78% were male. The baseline blood glucose was 10.8 ±4.1 in the infusion group and 11.1 ±3.5 in the control group (p = 0.23). **Stratification:** 1) known diabetes or admission blood glucose ≥ 11 | | | | | mortality<br>* adjusted for age, sex and cardiac intervention (PTCA or thrombolysis)<br><br>The mortality among patients with a mean 24h blood glucose ≥ 8.1 mmol/l was higher than those with mean blood glucose ≤ 8 mmol/l.<br>**Adverse events:**<br>There were 13 episodes of hypoglycaemia among the ITG and 2 episodes in the CTG (p = 0.02). No patient developed significant symptoms. | | variable rate insulin infusion protocol aimed at controlling hyperglycaemia did not reduce short term mortality following AMI using an intention to treat analysis. |

| Bibliographic Reference (Ref ID) | Study type/aim | Patient characteristics | Definitions | Intervention | Comparator | Length of follow-up | Outcome measures and effect size | Source of funding | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | mmol/litre without known diabetes (n = 142). 2) admission blood glucose 7.8-11 mmol/litre without known diabetes (n = 98). | | | | | | | |

**Mortality predictor tables**

**Independent associations between cardiovascular risk factors and glucometabolic markers with long-term mortality by multivariate Cox regression analysis. Observational data extracted from DIGAMI 1 study**

| | **Patient Groups** | | | | | |
|---|---|---|---|---|---|---|
| | **All (240 of 620)** | | **Control (138 of 314)** | | **Intensive insulin (102 of 306)** | |
| Parameter | RR (95% CI) | P | RR (95% CI) | P | RR (95% CI) | P |
| Age (1 added year) | 1.08 (1.06-1.11) | < 0.001 | 1.09 (1.06-1.12) | < 0.001 | 1.08 (1.05-1.12) | < 0.001 |
| Male sex | 1.12(0.82-1.54) | 0.46 | 0.97 (0.63-1.49) | 0.88 | 1.44 (0.88-2.32) | 0.15 |
| Previous disease<br>Myocardial infarction | 1.22 (0.87-1.70) | 0.25 | 1.10 (0.69-1.77) | 0.68 | 1.40 (0.86-2.28) | 0.16 |
| Congestive heart failure | 2.24 (1.60-3.14) | < 0.001 | 2.37 (1.50-3.74) | < 0.001 | 2.28 (1.33-3.73) | < 0.01 |
| Hypertension | 1.01 (0.75-1.35) | 0.96 | 1.15 (0.78-1.71) | 0.48 | 0.86 (0.55-1.36) | 0.52 |
| Smoker | 1.08 (0.69-1.68) | 0.74 | 1.05 (0.57-1.93) | 0.87 | 1.25 (0.62-2.52) | 0.53 |
| Diabetes duration (1 added year) | 1.02 (1.01-1.03) | < 0.01 | 1.01 (0.99-1.03) | 0.21 | 1.03 (1.01-1.05) | < 0.01 |
| Admission<br>Blood glucose +1mmol/l | 1.06 (1.03-1.10) | < 0.01 | 1.06 (1.01-1.11) | < 0.05 | 1.05 (0.99-1.11) | 0.065 |
| $HbA_{1c}$ +1% | 1.09 (1.00-1.18) | 0.054 | 1.15 (1.03-1.29) | < 0.05 | 1.03 (0.90-1.17) | 0.66 |

**Independent influence of different treatments on long-term mortality by multivariate Cox regression analysis correcting for age, sex and congestive heart failure during hospital stay. Observational data extracted from DIGAMI 1 study**

| | Patient Groups | | | | | |
|---|---|---|---|---|---|---|
| | All (240 of 620) | | Control (138 of 314) | | Intensive insulin (102 of 306) | |
| Parameter | RR (95% CI) | P | RR (95% CI) | P | RR (95% CI) | P |
| Intensive insulin treatment | 0.67 (0.51-0.88) | < 0.01 | - | - | - | - |
| Thrombolysis | 0.54 (0.41-0.72) | < 0.001 | 0.63 (0.43-0.92) | < 0.05 | 0.44 (0.28-0.72) | < 0.001 |
| β-Blockade at discharge | 0.68 (0.50-0.88) | < 0.01 | 0.55 (0.38-0.79) | < 0.01 | 0.81 (0.52-1.27) | 0.36 |
| ACE inhibitor at discharge | 1.36 (1.01-1.83) | < 0.05 | 1.50 (1.04-2.30) | < 0.05 | 1.20 (0.76-1.88) | 0.45 |

**Mortality when cohort divided into those with a mean glucose level in first 24 h above and below 8mmol/l. Observational data on mortality extracted from HI-5 STUDY**

| | 24h mean BGL < 8mmol/l | 24h mean BGL > 8mmol/l | Significance | Adjusted Odds ratio 95% CI | P Value |
|---|---|---|---|---|---|
| Inpatient Mortality | 0 | 7 | 0.05 | 7.2(0.9-58.9) | 0.07 |
| 3month mortality | 2 | 9 | 0.05 | 4.7(1.0-22.4) | 0.05 |
| 6 month mortality | 2 | 11 | 0.02 | 5.6(1.2-26.1) | 0.03 |

Adjusted for age, gender and cardiac intervention (PTCA or Thrombolysis)

**Mortality when cohort divided into those with a glucose level below 8mmol/l seven out of eight times and above 8mmol/l on more than 20% of the time when measured at 8 standard time points in the first 24 hours (0700, 0900,1200,1400,1700,1900,2200,0300). Observational data on mortality extracted from HI-5 STUDY**

| | Below 8mmol/l 7/8 times | Above 8mmol/l on more than 20% of the time | P Value |
|---|---|---|---|
| Inpatient mortality | 0% | 5.4% | 0.053 |
| 3 month mortality | 1.5% | 7.2% | 0.08 |
| 6 month mortality | 1.6% | 9.1% | 0.047 |

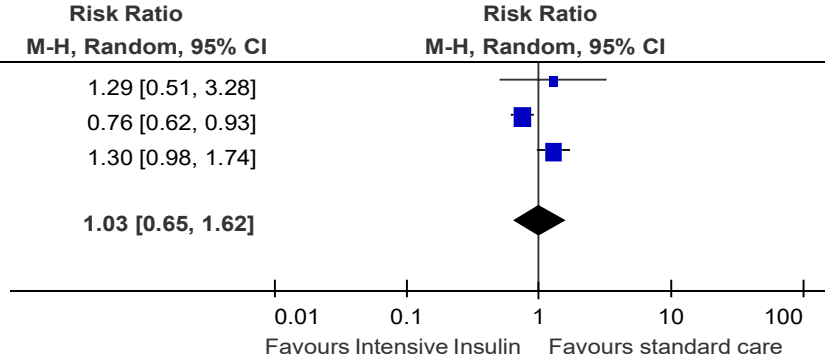
Adjusted for age, gender, diabetes status, creatine kinase, ST elevation infarct and randomisation group

## *Forest Plots for Review Question 1*

### Overall Mortality

| Study or Subgroup | Intensive Insulin therapy Events | Total | Standard Care Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Cheung 2006(103a) | 10 | 126 | 7 | 114 | 16.0% | 1.29 [0.51, 3.28] |
| Malmberg 1996(378) | 102 | 306 | 138 | 314 | 43.8% | 0.76 [0.62, 0.93] |
| Malmberg 2005(RefID) | 111 | 474 | 55 | 306 | 40.2% | 1.30 [0.98, 1.74] |
| **Total (95% CI)** | | **906** | | **734** | **100.0%** | **1.03 [0.65, 1.62]** |
| Total events | 223 | | 200 | | | |

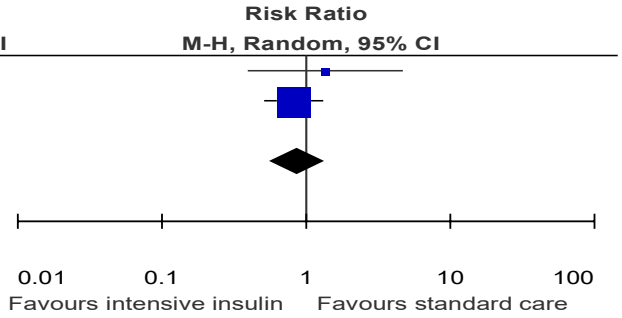
Heterogeneity: Tau² = 0.11; Chi² = 9.78, df = 2 (P = 0.008); I² = 80%
Test for overall effect: Z = 0.11 (P = 0.91)




### Inpatient Mortality

| Study or Subgroup | Intensive Insulin therapy Events | Total | Standard Care Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Cheung 2006(103a) | 6 | 126 | 4 | 114 | 12.6% | 1.36 [0.39, 4.69] |
| Malmberg 1995(396) | 28 | 306 | 35 | 314 | 87.4% | 0.82 [0.51, 1.32] |
| **Total (95% CI)** | | **432** | | **428** | **100.0%** | **0.87 [0.56, 1.36]** |
| Total events | 34 | | 39 | | | |

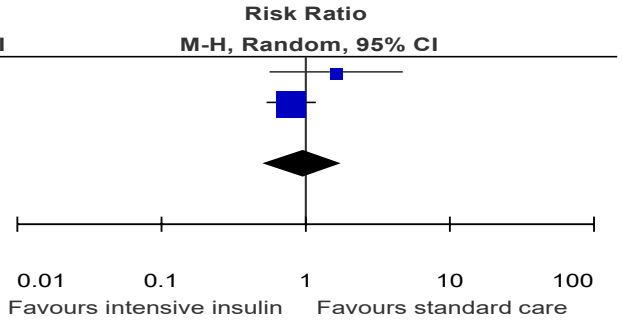
Heterogeneity: Tau² = 0.00; Chi² = 0.55, df = 1 (P = 0.46); I² = 0%
Test for overall effect: Z = 0.60 (P = 0.55)



## Three month Mortality

| Study or Subgroup | Intensive Insulin therapy Events | Total | Standard Care Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Cheung 2006(103a) | 9 | 126 | 5 | 114 | 25.3% | 1.63 [0.56, 4.72] |
| Malmberg 1995(396) | 38 | 306 | 49 | 314 | 74.7% | 0.80 [0.54, 1.18] |
| **Total (95% CI)** | | **432** | | **428** | **100.0%** | **0.95 [0.52, 1.76]** |
| Total events | 47 | | 54 | | | |

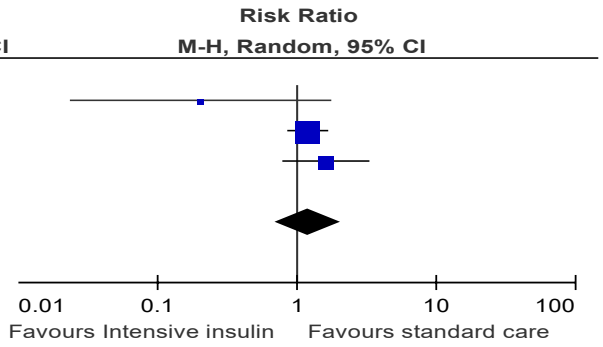
Heterogeneity: Tau² = 0.09; Chi² = 1.54, df = 1 (P = 0.22); I² = 35%
Test for overall effect: Z = 0.15 (P = 0.88)




## Reinfarction

| Study or Subgroup | Intensive Insulin therapy Events | Total | Standard Care Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Cheung 2006(103a) | 1 | 64 | 4 | 52 | 5.7% | 0.20 [0.02, 1.76] |
| Malmberg 1996(378) | 53 | 253 | 55 | 314 | 61.3% | 1.20 [0.85, 1.68] |
| Malmberg 2005(RefID) | 25 | 474 | 10 | 306 | 33.0% | 1.61 [0.79, 3.31] |
| **Total (95% CI)** | | **791** | | **672** | **100.0%** | **1.19 [0.70, 2.04]** |
| Total events | 79 | | 69 | | | |

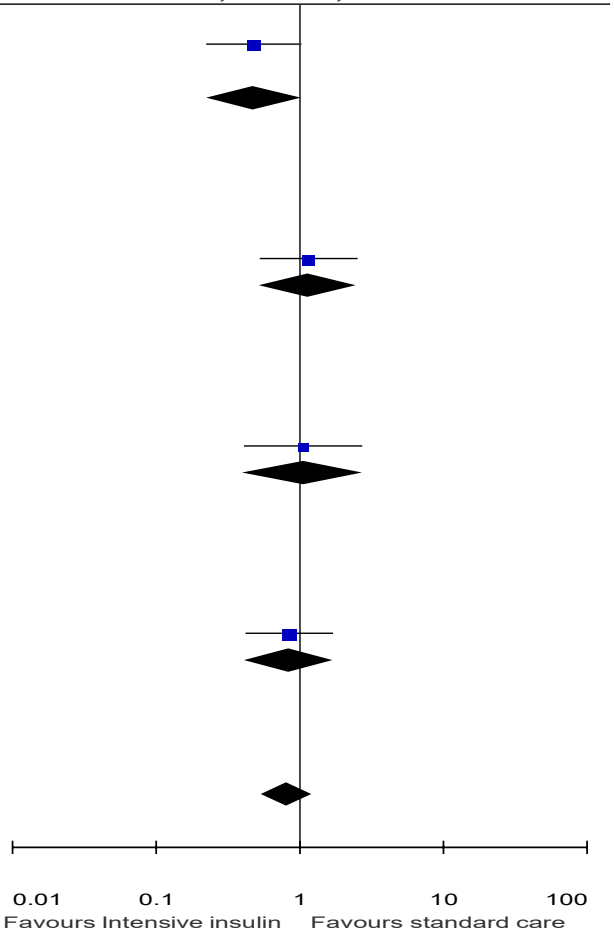
Heterogeneity: Tau² = 0.09; Chi² = 3.24, df = 2 (P = 0.20); I² = 38%
Test for overall effect: Z = 0.65 (P = 0.52)



## Three month mortality of subgroups stratified by risk

| Study or Subgroup | Intensive Insulin therapy Events | Total | Standard Care Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.5.1 no insulin low risk** | | | | | | |
| Malmberg 1995(396) | 9 | 139 | 18 | 133 | 26.4% | 0.48 [0.22, 1.03] |
| Malmberg 1995(396) | 0 | 0 | 0 | 0 | | Not estimable |
| **Subtotal (95% CI)** | | **139** | | **133** | **26.4%** | **0.48 [0.22, 1.03]** |
| Total events | 9 | | 18 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.89 (P = 0.06) | | | | | | |
| **1.5.2 no insulin high risk** | | | | | | |
| Malmberg 1995(396) | 11 | 63 | 10 | 66 | 25.1% | 1.15 [0.53, 2.52] |
| **Subtotal (95% CI)** | | **63** | | **66** | **25.1%** | **1.15 [0.53, 2.52]** |
| Total events | 11 | | 10 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.35 (P = 0.72) | | | | | | |
| **1.5.3 prev insulin low risk** | | | | | | |
| Malmberg 1995(396) | 7 | 54 | 8 | 65 | 17.1% | 1.05 [0.41, 2.72] |
| **Subtotal (95% CI)** | | **54** | | **65** | **17.1%** | **1.05 [0.41, 2.72]** |
| Total events | 7 | | 8 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.11 (P = 0.91) | | | | | | |
| **1.5.4 prev insulin high risk** | | | | | | |
| Malmberg 1995(396) | 11 | 50 | 13 | 50 | 31.4% | 0.85 [0.42, 1.71] |
| **Subtotal (95% CI)** | | **50** | | **50** | **31.4%** | **0.85 [0.42, 1.71]** |
| Total events | 11 | | 13 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.47 (P = 0.64) | | | | | | |
| **Total (95% CI)** | | **306** | | **314** | **100.0%** | **0.82 [0.55, 1.21]** |
| Total events | 38 | | 49 | | | |

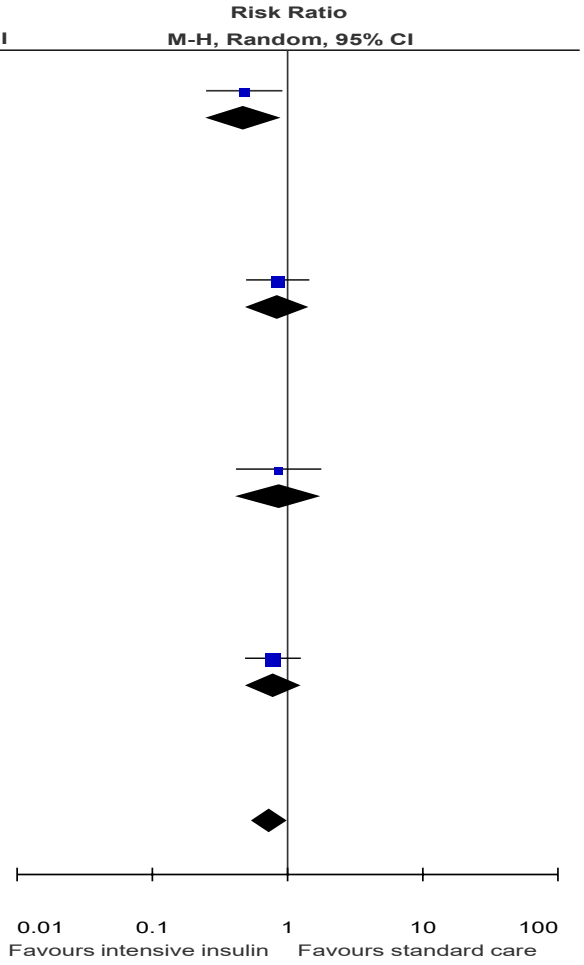
Heterogeneity: Tau² = 0.00; Chi² = 2.92, df = 3 (P = 0.40); I² = 0%
Test for overall effect: Z = 1.01 (P = 0.31)



## One year mortality of subgroups stratified by risk

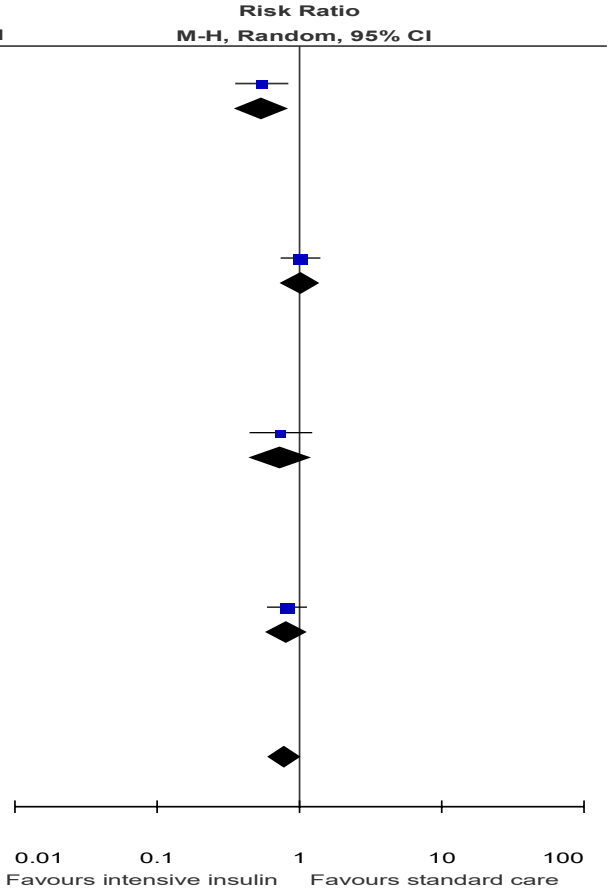
| Study or Subgroup | Intensive Insulin therapy Events | Total | Standard Care Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.6.1 no insulin low risk** | | | | | | |
| Malmberg 1995(396) | 12 | 139 | 24 | 133 | 19.5% | 0.48 [0.25, 0.92] |
| **Subtotal (95% CI)** | | **139** | | **133** | **19.5%** | **0.48 [0.25, 0.92]** |
| Total events | 12 | | 24 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 2.22 (P = 0.03) | | | | | | |
| **1.6.2 no insulin high risk** | | | | | | |
| Malmberg 1995(396) | 17 | 63 | 21 | 66 | 28.5% | 0.85 [0.50, 1.45] |
| **Subtotal (95% CI)** | | **63** | | **66** | **28.5%** | **0.85 [0.50, 1.45]** |
| Total events | 17 | | 21 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.60 (P = 0.55) | | | | | | |
| **1.6.3 prev insulin low risk** | | | | | | |
| Malmberg 1995(396) | 10 | 54 | 14 | 65 | 15.6% | 0.86 [0.42, 1.78] |
| **Subtotal (95% CI)** | | **54** | | **65** | **15.6%** | **0.86 [0.42, 1.78]** |
| Total events | 10 | | 14 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.41 (P = 0.68) | | | | | | |
| **1.6.4 prev insulin high risk** | | | | | | |
| Malmberg 1995(396) | 18 | 50 | 23 | 50 | 36.4% | 0.78 [0.49, 1.26] |
| **Subtotal (95% CI)** | | **50** | | **50** | **36.4%** | **0.78 [0.49, 1.26]** |
| Total events | 18 | | 23 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.01 (P = 0.31) | | | | | | |
| **Total (95% CI)** | | **306** | | **314** | **100.0%** | **0.74 [0.55, 0.98]** |
| Total events | 57 | | 82 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 2.22, df = 3 (P = 0.53); I² = 0%
Test for overall effect: Z = 2.07 (P = 0.04)
Test for subgroup differences: Not applicable



## Long term mortality (follow up 3.4 years) of subgroups stratified by risk

| Study or Subgroup | Intensive Insulin therapy Events | Total | Standard Care Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.7.1 no insulin low risk** | | | | | | |
| Malmberg 1995(396) | 25 | 139 | 44 | 133 | 22.2% | 0.54 [0.35, 0.84] |
| **Subtotal (95% CI)** | | **139** | | **133** | **22.2%** | **0.54 [0.35, 0.84]** |
| Total events | 25 | | 44 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 2.78 (P = 0.005) | | | | | | |
| **1.7.2 no insulin high risk** | | | | | | |
| Malmberg 1995(396) | 34 | 63 | 35 | 66 | 30.0% | 1.02 [0.74, 1.40] |
| **Subtotal (95% CI)** | | **63** | | **66** | **30.0%** | **1.02 [0.74, 1.40]** |
| Total events | 34 | | 35 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.11 (P = 0.91) | | | | | | |
| **1.7.3 prev insulin low risk** | | | | | | |
| Malmberg 1995(396) | 16 | 54 | 26 | 65 | 18.0% | 0.74 [0.45, 1.23] |
| **Subtotal (95% CI)** | | **54** | | **65** | **18.0%** | **0.74 [0.45, 1.23]** |
| Total events | 16 | | 26 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.16 (P = 0.25) | | | | | | |
| **1.7.4 prev insulin high risk** | | | | | | |
| Malmberg 1995(396) | 27 | 50 | 33 | 50 | 29.8% | 0.82 [0.59, 1.13] |
| **Subtotal (95% CI)** | | **50** | | **50** | **29.8%** | **0.82 [0.59, 1.13]** |
| Total events | 27 | | 33 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.21 (P = 0.22) | | | | | | |
| **Total (95% CI)** | | **306** | | **314** | **100.0%** | **0.78 [0.60, 1.02]** |
| Total events | 102 | | 138 | | | |
| Heterogeneity: Tau² = 0.03; Chi² = 5.65, df = 3 (P = 0.13); I² = 47% | | | | | | |
| Test for overall effect: Z = 1.81 (P = 0.07) | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | |



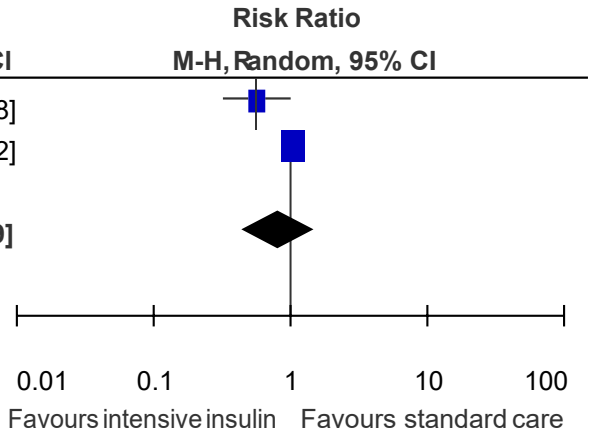

**High risk: At least two of the following: Above 70 years, previous Myocardial infarction, previous congestive heart failure and current treatment with digitalis(digoxin)**

## Heart Failure

| Study or Subgroup | Intensive Insulin therapy Events | Total | Standard Care Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Cheung 2006(103a) | 16 | 126 | 26 | 114 | 40.4% | 0.56 [0.32, 0.98] |
| Malmberg 1995(396) | 153 | 306 | 151 | 314 | 59.6% | 1.04 [0.89, 1.22] |
| **Total (95% CI)** | | **432** | | **428** | **100.0%** | **0.81 [0.44, 1.49]** |
| Total events | 169 | | 177 | | | |

Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 4.42$, df = 1 (P = 0.04); $I^2 = 77\%$

Test for overall effect: Z = 0.68 (P = 0.49)

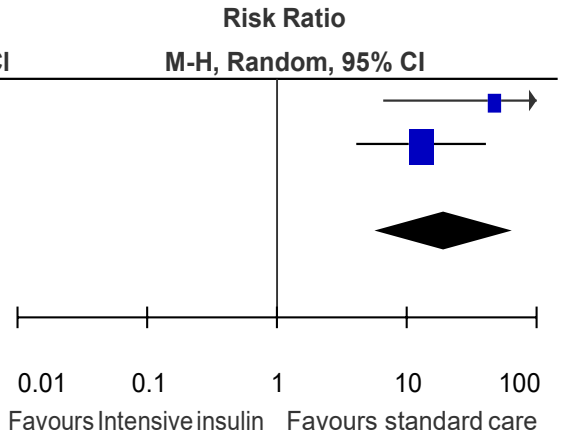


## Hypoglycaemia after 24 hours

| Study or Subgroup | Intensive Insulin therapy Events | Total | Standard Care Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Malmberg 1995(396) | 46 | 306 | 1 | 315 | 31.0% | 47.35 [6.57, 341.22] |
| Malmberg 2005(RefID) | 60 | 474 | 3 | 306 | 69.0% | 12.91 [4.09, 40.80] |
| **Total (95% CI)** | | **780** | | **621** | **100.0%** | **19.32 [5.79, 64.41]** |
| Total events | 106 | | 4 | | | |

Heterogeneity: Tau² = 0.20; Chi² = 1.30, df = 1 (P = 0.25); I² = 23%

Test for overall effect: Z = 4.82 (P < 0.00001)

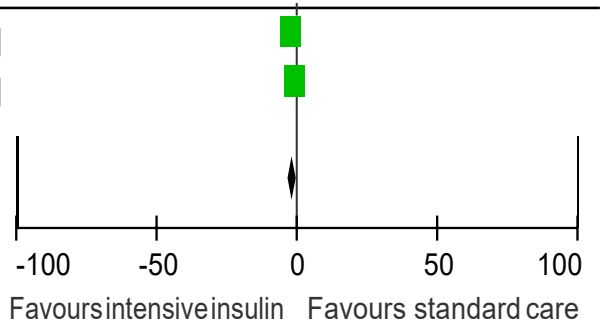


Difference in Blood glucose levels after 24 hours

| | Intensive insulin | | | standard care | | | | Mean Difference | Mean Difference |
|---|---|---|---|---|---|---|---|---|---|
| **Study or Subgroup** | **Mean** | **SD** | **Total** | **Mean** | **SD** | **Total** | **Weight** | **IV, Random, 95% CI** | **IV, Random, 95% CI** |
| Malmberg 1995(396) | 9.6 | 3.3 | 306 | 11.7 | 4.1 | 314 | 49.0% | -2.10 [-2.69, -1.51] | |
| Malmberg 2005(RefID) | 9.1 | 3 | 474 | 10 | 3.6 | 306 | 51.0% | -0.90 [-1.39, -0.41] | |
| **Total (95% CI)** | | | **780** | | | **620** | **100.0%** | **-1.49 [-2.66, -0.31]** | |

Heterogeneity: Tau² = 0.64; Chi² = 9.57, df = 1 (P = 0.002); I² = 90%

Test for overall effect: Z = 2.48 (P = 0.01)



## *Review question 2: What is the optimal inpatient metabolic management of patients presenting with hyperglycaemia and acute coronary syndrome (ACS) without a diagnosis of diabetes mellitus?*

### Evidence table 2

<table>
<tr><th>Study ref (Ref ID)</th><th>Study type/aim</th><th>Patient characteristics</th><th>Definitions</th><th>Intervention</th><th>Comparator</th><th>Length of follow-up</th><th>Outcome measures and effect size</th><th>Source of funding</th><th>Comments</th></tr>
<tr>
<td>Weston et al 2007 (Ref ID:312a)</td>
<td>An observational study from the MINAP database to determine the effect of insulin for the management of hyperglycaemia in non-diabetic patients with ACS.</td>
<td>2642 patients (any insulin treatment = 872, no treatment = 1770). The following patient characteristics were reported mean age (insulin = 72 yrs, no treatment = 76 yrs). Admission blood glucose was also recorded for each group; insulin = 14.8 mmol/l (12.3-18.6), no</td>
<td><u>Hyperglycaemia:</u> study included patients without a diagnosis of diabetes and who presented to hospital with ACS and an admission blood glucose of ≥ 11.0 mmol/l</td>
<td><u>Insulin:</u> The majority of those receiving insulin were given the DIGAMI insulin/glucose regime 607/872 (69.6%) or an insulin pump 225/872 (25.8%). The remaining 40 (4.6%) insulin treated patients</td>
<td><u>No treatment:</u> no diabetic treatment in hospital and treatment strategy was not recorded.</td>
<td>There was an absence of follow-up data so analyses of outcomes were based on an assumption that medication prescribed at discharge was continued after discharge.</td>
<td><u>Mortality at 7 and 30 days:</u><br>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 also performed after excluding 79 deaths occurring on the day of admission (median interval 12 hours). The adjusted RR of death was slightly reduced, but remained statistically significant (see table below).
<table>
<tr><th>All deaths</th><th>No treatment (%)</th><th>Insulin</th><th>RR</th><th>Adjusted RR*</th><th>P-value</th></tr>
<tr><td>7 days</td><td>290/1761 (16.5)</td><td>101/868 (11.6)</td><td>1.42</td><td>1.56</td><td>< 0.001</td></tr>
<tr><td>30 days</td><td>389/1761 (22.1)</td><td>137/868 (15.8)</td><td>1.40</td><td>1.51</td><td>< 0.001</td></tr>
<tr><td colspan="6">Deaths on day of admission excluded</td></tr>
</table>
</td>
<td>The Healthcare Commissions.</td>
<td>Mortality at 7 and 30 days compared those who were treated with insulin (this was by any regime) with those who did not receive any treatment and those who did not have treatment recorded. The authors concluded that non-diabetic patients presenting with hyperglycaemia in association with ACS have</td>
</tr>
</table>

<table>
<tr><th>Study ref (Ref ID)</th><th>Study type/aim</th><th>Patient characteristics</th><th>Definitions</th><th>Intervention</th><th>Comparator</th><th>Length of follow-up</th><th>Outcome measures and effect size</th><th>Source of funding</th><th>Comments</th></tr>
<tr>
<td></td>
<td></td>
<td>treatment = 12.9 (11.7-14.9) and treatment strategy not recorded = 13.0 (12.0-16.0). Gender, ST elevation infarction, length of stay, admission cholesterol, heart rate on admission, blood pressure and current smoking habits are also presented</td>
<td></td>
<td>received single dose insulin regimes.</td>
<td></td>
<td></td>
<td>
<table>
<tr><td>1-7 days</td><td>228/1682 (13.6)</td><td>80/841 (9.5)</td><td>1.43</td><td>1.43</td><td>0.011</td></tr>
<tr><td>1-30 days</td><td>327/1682 (19.4)</td><td>116/841 (13.8)</td><td>1.41</td><td>1.41</td><td>0.004</td></tr>
</table>
* adjustments for age, gender, HF, renal failure, admission blood glucose, presence of ST elevation infarction and history of previous angina or MI<br><br>
The effect of insulin treatment on risk of death was examined separately for ST segment (STEMI) and non-ST segment elevation infarction (NSTEMI).<br>
7 and 30 day mortality by AMI type:
<table>
<tr><th>MI type</th><th>No treatment (%)</th><th>Insulin (%)</th><th>RR</th><th>Adjusted RR</th><th>P-value</th></tr>
<tr><td>STEMI (7 days)</td><td>164/755 (21.7)</td><td>67/509 (13.2)</td><td>1.64</td><td>1.62</td><td>0.003</td></tr>
<tr><td>STEMI (30 days)</td><td>193/755 (25.6)</td><td>80/509 (15.7)</td><td>1.63</td><td>1.58</td><td>0.002</td></tr>
<tr><td>NSTEMI (7 days)</td><td>126/1006 (12.5)</td><td>34/359 (9.5)</td><td>1.32</td><td>1.30</td><td>0.211</td></tr>
<tr><td>NSTEMI (30 days)</td><td>196/1006 (19.5)</td><td>57/359 (15.9)</td><td>1.23</td><td>1.25</td><td>0.188</td></tr>
</table>
</td>
<td></td>
<td>a better short-term prognosis when they are treated with insulin.</td>
</tr>
</table>

| Study ref (Ref ID) | Study type/aim | Patient characteristics | Definitions | Intervention | Comparator | Length of follow-up | Outcome measures and effect size | Source of funding | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | * covariates as described above were used for adjustments. For STEMI patients the use of reperfusion was added as they were more likely to receive reperfusion.<br>The crude mortality was greater in both groups for patients who did not receive insulin, but the mortality difference between insulin-treated and those without treatment was more marked for patients with STEMI. The adjusted RR for those with NSTEMI who did not receive insulin was also greater, but this did not achieve statistical significance. | | |

| Study ref (Ref ID) | Study type/aim | Patient characteristics | Definitions | Intervention | Comparator | Length of follow-up | Outcome measures and effect size | Source of funding | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Cheung et al 2006 (Ref ID: 103a) | The HI-5 study was a multicenter open-label randomised controlled trial aimed to determine whether tight glycaemic control improves outcomes for hyperglycaemic patients with AMI | 240 patients (126 in infusion therapy group and 114 in conventional therapy group). **Inclusion criteria:** 1) evidence of AMI within last 24 hours and 2) known diabetes or not diabetic with an admission blood glucose level ≥ 7.8mmol/litre (140mg/dl). **Baseline characteristics:** There were no differences in baseline characteristics. There was no difference between patients given | **Hypoglycaemia:** finger prick blood glucose < 3.5mmol/l, irrespective of the occurrence of symptoms. **Reinfarction:** new AMI occurring > 72 hours following index infarct. Cardiac failure: dyspnoea with radiographic evidence of pulmonary or interstitial edema. **Cardiogenic shock:** cardiac | **Infusion Therapy Group (ITG):** patients placed on insulin at 2 units/h and 5% dextrose at 80ml/h. Insulin was titrated to maintain blood glucose between 4 and 10mmol/litre for at least 24 hours. For patients with cardiac failure, 10% dextrose was administered at 40 | **Conventional Therapy Group (CTG):** remained on their usual diabetes therapy but metformin was temporarily discontinued. Supplemental subcutaneous short-acting insulin was permitted if blood glucose was > 16mmol/l | Patients were contacted to obtain information regarding the occurrence of cardiovascular events following discharge. Outcomes were measured during the index hospital admission and after 3 and 6 months. There was no information relating to mean follow-up period but | **Sub-group analysis by diabetes status:** Among patients with diabetes there was a lower reinfarction rate in the ITG (0 vs.7.7%, p = 0.04) and a lower occurrence of composite end points (21.9 vs. 40.4%, p = 0.03) at 3 months. There were no differences in other outcome variables. Among those without diabetes, there was an incidence of cardiac failure in the ITG during the inpatient period (11.3 vs. 27.4%, p = 0.02). There were no differences in other outcome variables | National Health and Medical Research Council of Australia Project Grant and Novo Nordisk Pharmaceuticals | Data for glycaemic control in the first 24 hours were collected for 97.5% of patients. The mean 24 hr blood glucose was distributed around a median level of 8.1mmol/l so the cohort was divided into ≤ 8 mmol/l and ≥ 8.1mmol/l. The authors concluded that insulin infusion did not reduce short-term mortality following AMI using an intention to treat analysis. The mean duration of symptom onset to |

| Study ref (Ref ID) | Study type/aim | Patient characteristics | Definitions | Intervention | Comparator | Length of follow-up | Outcome measures and effect size | Source of funding | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | PTCA (infusion = 32%, control = 39%), thrombolysis (32% vs. 32%) or no reperfusion (37% vs. 29%). The mean age was 63 ± 11 years and 116 (48%) participants had known diabetes (all type 2). 78% were male. The baseline blood glucose was 10.8 ±4.1 in the infusion group and 11.1 ±3.5 in the control group (p = 0.23). **Stratification:** 1) known diabetes or admission | failure with a systolic blood pressure < 80mmHg. **Composite end point:** death or any major cardiac event. **Evidence of AMI:** troponin-T > 0.1 µg/l or electrographic criteria of ST elevation in two limb leads. | ml/h. All diabetes medications were discontinued temporarily. Upon cessation of infusion, patients resumed their usual diabetes medication. | | at 3 months 125 and 112 patients in the intervention and standard care group were assessed and at 6 months 121 and 109 were assessed in the intervention and standard care group. | | | commencement of insulin was 13 hrs and this may have been too late for significant myocardial salvage. The authors concluded that a variable rate insulin infusion protocol aimed at controlling hyperglycaemia did not reduce short term mortality following AMI using an intention to treat analysis. |

| Study ref (Ref ID) | Study type/aim | Patient characteristics | Definitions | Intervention | Comparator | Length of follow-up | Outcome measures and effect size | Source of funding | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | blood glucose ≥ 11 mmol/litre without known diabetes (n = 142). 2) admission blood glucose 7.8-11 mmol/litre without known diabetes (n = 98). | | | | | | | |
| Van der Horst et al 2003 (Ref ID: 5001) | Single-center randomised controlled trial to investigate whether adjunction of glucose-insulin-potassium (GIK) infusion to primary coronary transluminal angioplasty (PTCA) is | 940 patients (infusion = 476, control = 464). **Inclusion criteria:** all patients with symptoms consistent with AMI of > 30 mins, presenting within 24 hours after the onset of symptoms and with ST elevation of more than | | **GIK infusion:** a continuous infusion of 80 mmol potassium chloride in 500ml 20% glucose with a rate of 3 ml/kg body weight /hr over an 8 to 12 hr period was given as | **Non-infusion group:** no details given | Main outcome was 30-day mortality. No further details were given on mean follow-up period. | Results are based on sub-group analysis by diabetes status, however outcomes for reinfarction and composite end-point are based on all patients<br>**30-day mortality:**<br>23 patients (4.8%) in the GIK group vs. 27 (5.8%) in the control group had died at 30 days (RR 0.82, CI 0.46-1.46, p = 0.50). In 856/940 patients without signs of heart failure (Killip class 1), the mortality rate was 5/426 (1.2%) in the GIK group versus 18/430 patients (4.2%) in the control group (RR 0.28, CI 0.1-0.75, p = 0.01). In this subgroup of patients, a higher number of patients died of HF in the control group (0.7% in GIK group vs. 2.8% in the control group). Non-significant differences between the GIK and control groups were also found for sub groups based on age ( < 60 years and ≥ 60 | Not reported. | The authors concluded that GIK as adjunctive therapy to PTCA in AMI did not result in a significant mortality reduction in all patients. However, in the large subgroup of patients without signs of HF (over 90% of the population), a significant |

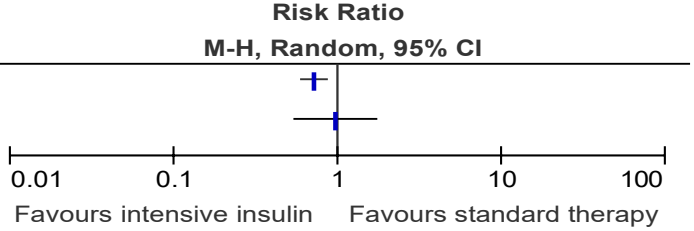
| Study ref (Ref ID) | Study type/aim | Patient characteristics | Definitions | Intervention | Comparator | Length of follow-up | Outcome measures and effect size | Source of funding | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | effective in patients with AMI. | 1mm in 2 or more leads or new onset left bundle branch block were evaluated for inclusion. **Baseline characteristics:** With the exception of male gender, there were no statistically significant differences between both groups. After coronary angioplasty, 90.5% underwent PTCA, 4% were referred for CABG within 7 days after initial stabilisation and 4.5% were treated conservatively | | soon as possible. A continuous infusion of short acting insulin (50 U Actrapid HM, Novo Nordisk, Copenhagen Denmark) in 50 ml 0.9% sodium chloride was started using a pump (Perfusor-FM, B. Braun Germany). Baseline infusion-infusion dose and hourly adjustment | | | years), gender, time to admission ( ≤ 180 mins and > 180 mins) and diabetes status (with diabetes RR = 0.30, 0.06-1.56, p = 0.16, without diabetes RR = 0.97, 0.52-1.81, p = 1.00).<br>**Clinical end-points at 30 days:**<br>There were no significant differences between the GIK group and control group in terms of recurrent infarction (adj RR 0.42, CI 0.12-1.5, p = 0.19), repeat angioplasty (adj RR 0.74, CI 0.38-1.44, p = 0.37) and composite end point (adj RR 0.68, CI 0.44-1.05, p = 0.08). However, In patients without HF (Killip class 1), the composite end point showed a significant advantage of GIK (adj RR 0.47, CI 0.27-0.83, p = 0.01). In this group without HF there was also a beneficial effect of GIK on mortality (adj RR 0.28, CI 0.10-0.77, p = 0.01).<br>**Adverse events:**<br>Side effects such as hypoglycaemia, hyperkaliemia and severe phlebitis were not observed.<br>**Blood glucose levels:**<br>There were no major differences in blood glucose levels between the GIK group and control group at admission (median blood glucose 8.5 mmol/l in both groups) and 16 hours after admission (median blood glucose 7.7 mmol/l in the GIK and 8.1 mmol/l in the control group) | | reduction was seen. |

| Study ref (Ref ID) | Study type/aim | Patient characteristics | Definitions | Intervention | Comparator | Length of follow-up | Outcome measures and effect size | Source of funding | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | (there were no sig differences between groups). 50 (10.5%) in infusion group and 49 (10.6%) in control group had diabetes. | | s of the insulin dose were based on a normogram to obtain blood glucose levels between 7.0 and 11.0 mmol/l. | | | | | |

## *Forest plots for Review Question 2*

Forest plot of 30 day mortality in patients without diagnosed diabetes

| Study or Subgroup | Intensive insulin Events | Total | Standard care Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| MINAP (Weston 2007) | 116 | 841 | 327 | 1682 | | 0.71 [0.58, 0.86] |
| Van Der Horst 2003 | 21 | 426 | 21 | 415 | | 0.97 [0.54, 1.76] |

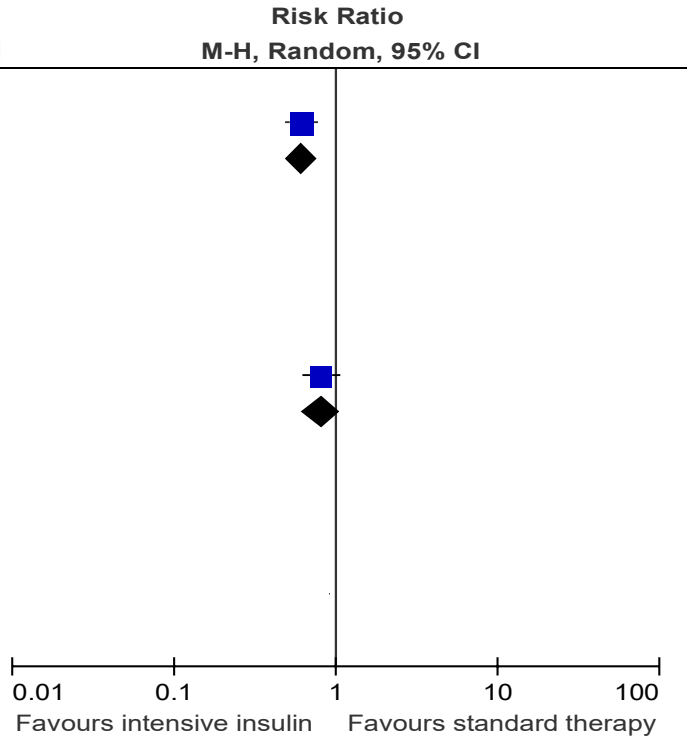



Interpretation

The forest plot above shows a significant 29% reduction in mortality in patients without diabetes who were administered intensive insulin in comparison to standard therapy using observational data from MINAP (deaths on day of admission were excluded). However, the RCT (Van der Horst 2003) shows no significant reduction in mortality in patients without previous diabetes who were given intensive insulin in comparison to standard therapy. The HI-5 study (Cheung et al 2006) reported that subgroup analysis by diabetes status showed no differences in mortality at any stage. These studies were not combined to provide a single summary estimate as there is a high risk of heterogeneity. The intervention in the Van der Horst paper was glucose-insulin-potassium infusion while the MINAP cohort received any insulin intervention (approx 70% were given the glucose-insulin regime as used in the DIGAMI study). It should also be noted that the relative risks used in the forest plot relate to crude unadjusted estimates (available adjusted values will be presented in GRADE where possible).

## Forest plot of 30 day mortality, sub-grouped by type of infarction

| Study or Subgroup | Intensive insulin Events | Total | Standard care Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.3.1 STEMI** | | | | | | |
| MINAP (Weston 2007) | 80 | 509 | 193 | 755 | 52.8% | 0.61 [0.49, 0.78] |
| **Subtotal (95% CI)** | | **509** | | **755** | **52.8%** | **0.61 [0.49, 0.78]** |
| Total events | 80 | | 193 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 4.05 (P < 0.0001) | | | | | | |
| **1.3.2 NSTEMI** | | | | | | |
| MINAP (Weston 2007) | 57 | 359 | 196 | 1006 | 47.2% | 0.81 [0.62, 1.07] |
| **Subtotal (95% CI)** | | **359** | | **1006** | **47.2%** | **0.81 [0.62, 1.07]** |
| Total events | 57 | | 196 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.49 (P = 0.14) | | | | | | |

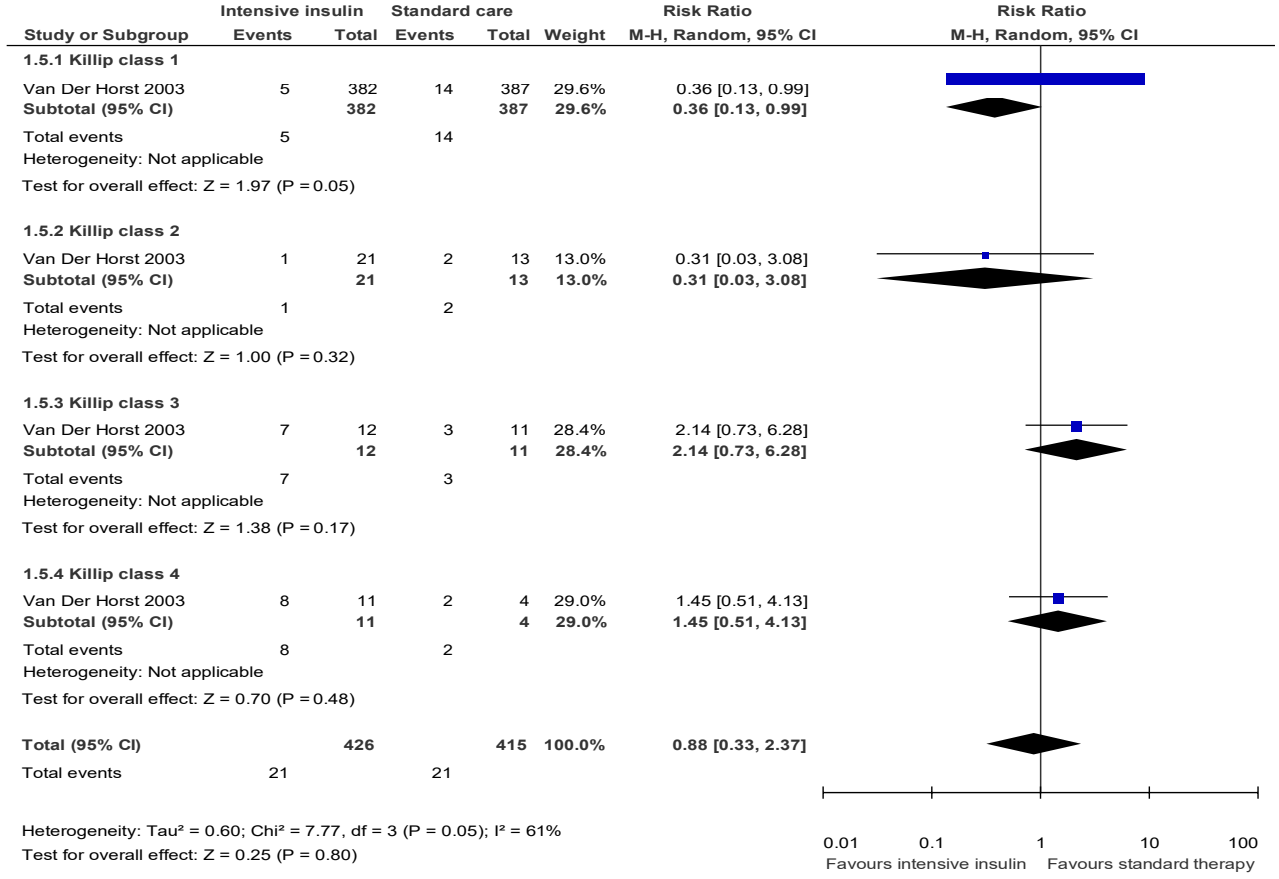



## Interpretation

The forest plot above illustrates a statistically significant 39% reduction in overall mortality (after 30 days) in patients who had a STEMI and were administered intensive insulin in comparison to no diabetic therapy. There was no significant effect for patients who had an NSTEMI. Th is suggests that intensive therapy may be more effective in reducing mortality in patients who have had a STEMI in comparison to an NSTEMI.

However, it should be noted that this is a sub-group analysis from a single observational study and may be prone to bias, therefore needs to be interpreted with caution. The relative risks used in the forest plot relate to crude unadjusted estimates.

## Forest plot of 30 day mortality, sub-grouped by Killip class

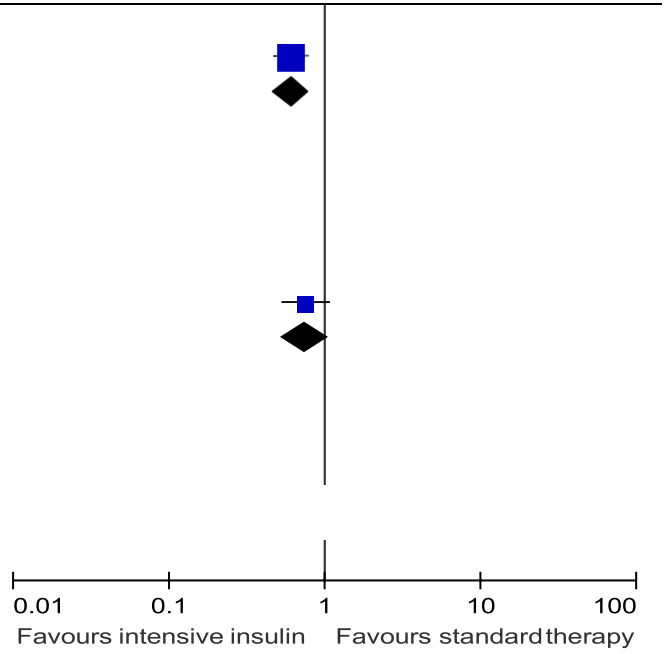


Interpretation

The forest plot above shows that the only statistically significant reduction in mortality occurred in patients without previous diabetes who were classified as having Killip class 1 (no clinical signs of heart failure). The other groups (that indicate increasing risk of heart failure) showed no significant effect of intensive insulin on risk of death. As above it should be noted that this is a sub-group analysis from a single trial and may be prone to bias, therefore needs to be interpreted with caution. The relative risks used in the forest plot relate to crude unadjusted estimates.

Forest plot of 7 day mortality by type of infarction

| Study or Subgroup | Intensive insulin Events | Total | Standard care Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.4.1 STEMI** | | | | | | |
| MINAP (Weston 2007) | 67 | 509 | 164 | 755 | 65.4% | 0.61 [0.47, 0.79] |
| **Subtotal (95% CI)** | | **509** | | **755** | **65.4%** | **0.61 [0.47, 0.79]** |
| Total events | 67 | | 164 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 3.76 (P = 0.0002) | | | | | | |
| **1.4.2 NSTEMI** | | | | | | |
| MINAP (Weston 2007) | 34 | 359 | 126 | 1006 | 34.6% | 0.76 [0.53, 1.08] |
| **Subtotal (95% CI)** | | **359** | | **1006** | **34.6%** | **0.76 [0.53, 1.08]** |
| Total events | 34 | | 126 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.53 (P = 0.13) | | | | | | |



## Interpretation

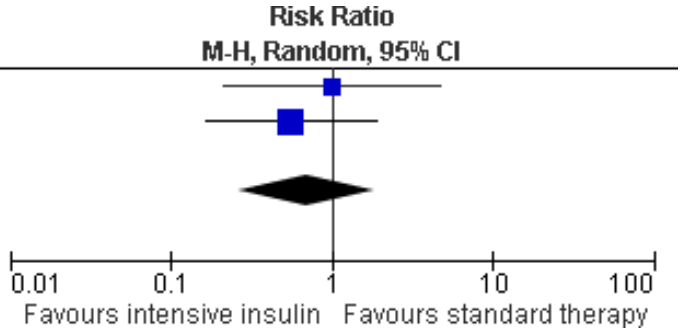
The forest plot above shows a significant 39% reduction in mortality at 7 days in patients who had a STEMI and were administered intensive insulin in comparison to standard therapy. There was no significant reduction in mortality for patients who had a NSTEMI and were given intensive insulin treatment in comparison to standard therapy. This is a sub-group analysis from a single observational study and may be prone to bias. It should also be noted that the relative risks used in the forest plot relate to crude unadjusted estimates.

## Forest plot of reinfarction (after up to 3 months)

| | Intensive insulin | | Standard therapy | | | Risk Ratio |
|---|---|---|---|---|---|---|
| **Study or Subgroup** | **Events** | **Total** | **Events** | **Total** | **Weight** | **M-H, Random, 95% CI** |
| HI-5 (Cheung 2006) | 3 | 62 | 3 | 62 | 38.0% | 1.00 [0.21, 4.76] |
| Van Der Horst 2003 | 4 | 476 | 7 | 464 | 62.0% | 0.56 [0.16, 1.89] |
| **Total (95% CI)** | | **538** | | **526** | **100.0%** | **0.70 [0.27, 1.82]** |
| Total events | 7 | | 10 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 0.34, df = 1 (P = 0.56); I² = 0%

Test for overall effect: Z = 0.74 (P = 0.46)




## Interpretation

The forest plot above shows no significant reduction in reinfarction. It should be noted that for this outcome the Van der Horst paper included some patients with diabetes (10%, n = 99) and crude unadjusted estimates of relative risks have been presented here for this study.

## *Review question 3: At what stage should patients with hyperglycaemia and ACS without diagnosed diabetes be referred for subsequent investigations for possible diabetes?*

### Evidence table 3

<table>
<tr><th>Bibliography (Ref ID)</th><th>Study type/aim</th><th>Number of patients and characteristics</th><th>Definitions and outcome measures</th><th>Risk factors/results</th><th>Length of follow-up</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr>
<td>Tenerz et al 2003 (1593)</td>
<td>To characterise the glucometabolic profile of patients with AMI without diabetes and to see if sustained glucometabolic perturbations are predictable during the hospital phase of the disease.</td>
<td>145 patients with AMI and no previous diagnosis of diabetes were defined as having normal glucose tolerance (NGT, 34%, n = 61, mean age 50), impaired glucose tolerance (IGT, 41%, n = 59, mean age 64) or diabetes (25%, n = 36, mean age 65). Treatment for hypertension</td>
<td>During hospitalisation FBG was measured on first morning after admission. OGTT performed immediately before discharge (usually on day 5) and repeated 3 months after hospital discharge. OGTT including FBG and blood glucose measurement after 60 (BG-60) and 120 mins (BG-120). Classifications were based on</td>
<td><u>Blood glucose levels at admission (first morning) and discharge (usually day 5)</u>
<table>
<tr><th>Blood glucose (mmol/litre)</th><th>NGT</th><th>IGT</th><th>Diabetes</th><th>P valu</th></tr>
<tr><td>Admission</td><td>6.0 (1.4)</td><td>6.2 (1.6)</td><td>7.1 (2.2)</td><td>0.04</td></tr>
<tr><td>Discharge</td><td>5.0 (0.65)</td><td>5.1 ( .93</td><td>5.6 (0.83</td><td>0.00</td></tr>
</table>
Data are median (interquartile range)<br>
Blood glucose for all patients taken together decreased during hospital stay with no further decrease until follow-up.<br>
<u>Results of OGTT in patients with AMI at discharge from hospital and 3 months after (n = 142)</u>
<table>
<tr><th></th><th></th><th colspan="3">OGTT at 3 months</th></tr>
<tr><th></th><th>OGTT at discharge</th><th>NGT</th><th>IGT</th><th>Diabetes</th></tr>
<tr><td>NGT</td><td>48 (100)</td><td>23 (48)</td><td>23 (48)</td><td>2 (4)</td></tr>
<tr><td>IGT</td><td>47 (100)</td><td>18 (38)</td><td>21 (45)</td><td>8 (17)</td></tr>
<tr><td>Diabetes</td><td>47 (100)</td><td>7 (15)</td><td>15 (32)</td><td>25 (53)</td></tr>
</table>
Data are n (%)</td>
<td>3 month follow-up (142 results available for OGTT after 3 months- no further details given for drop-outs)</td>
<td>Swedish Heart-Lung Foundation, the Swedish Medical Research Council and the Center for Clinical Research, Central Hospital, Vasteras, Uppsala University, the research foundation of Vastmanland county council, the Karolinska Institute and Aventis U.S</td>
<td>Authors conclude that readily available routine tests such as an OGTT or a single blood glucose value taken 60 minutes after ingestion of 75g glucose at discharge predict the diagnosis of abnormal glucose tolerance after 3 months. Other components</td>
</tr>
</table>

| Bibliography (Ref ID) | Study type/aim | Number of patients and characteristics | Definitions and outcome measures | Risk factors/results | Length of follow-up | Source of funding | Additional comments |
|---|---|---|---|---|---|---|---|
| | | was most common amongst those with IGT. **Exclusion:** known diabetes and residence outside catchment area | WHO definitions from 1998. **Normal glucose tolerance (NGT):** fasting blood glucose (FBG) < 6.1mmol/litre, 120 minute blood glucose (BG-120) < 7.8mmol/litre **Impaired glucose tolerance:** FBG < 6.1mmol/litre, BG-120 7.8-11.0mmol/litre **Diabetes:** FBG ≥ 6.1mmol/litre and/or BG-120 ≥ 11.1mmol/litre | **Agreement** 49% of the OGTT performed at discharge and after 3 months allocated the patients into the same glucose tolerance category (NGT, IGT or diabetes) on both occasions. The agreement between the OGTT classification at discharge and after 3 months could be expressed as k = 0.23 (p < 0.001). **Predictors of abnormal glucose tolerance** The hospital derived variables that predicted diabetes after 3 months were OGTT (p = 0.001) and a single BG-60 (p = 0.008). Adding age, BMI, antihypertensive treatment, and $HbA_{1c}$ at admission, fasting triglycerides or HDL cholesterol on day 2, and a single FBG, fasting insulin, fasting proinsulin, HOMA-IR, and PAI-1 on day 5 to the logical regression model did not improve the predictive value. BG-60 was the only predictive variable (P < 0.001) when a similar analysis was performed aiming at the prediction of IGT or diabetes after 3 months. The odds ratio for a 1 mmol/litre increase in BG-60 was 1.38 (CI 1.16-1.64). With a cutoff value of 8.6mmol/litre for BG-60, 70% of the patients were correctly predicted as either belonging to the NGT group or the IGT/diabetes group after 3 months, using cross-validation. | | | of the metabolic syndrome do not add further predictive value. |
| Ishihara et al 2006 | To investigate whether | 200 non-diabetic | Plasma glucose was measured at | **Results of OGTT at admission and at discharge (1 week after admission)** | Only assessed | No financial support for | Authors conclude that |

<table>
<tr><th>Bibliography (Ref ID)</th><th>Study type/aim</th><th>Number of patients and characteristics</th><th>Definitions and outcome measures</th><th>Risk factors/results</th><th>Length of follow-up</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr>
<td>(634)</td>
<td>admission hyperglycaemia in non-diabetic patients with AMI is a surrogate for previously undiagnosed abnormal glucose tolerance</td>
<td>patients with AMI were categorised at admission into 3 groups:<br><u>Group 1</u>: (no or mild admission hyperglycaemia < 7.8 mmol/litre)<br><u>Group 2:</u><br>(moderate admission hyperglycaemia ≥ 7.8 and < 11.1 mmol/litre)<br><u>Group 3:</u><br>(severe admission hyperglycaemia ≥ 11.1mmol/litre).<br><u>Exclusions:</u> patients with previous diagnosis of</td>
<td>time of hospital admission and patients were divided into groups 1, 2 or 3. OGTT was performed before hospital discharge (one week after admission). Definitions were<br>according to WHO 1998. The American Diabetes Association (ADA) criteria for diabetes were also assessed.<br><u>Diabetes:</u> FBG ≥ 7.0mmol/litre and/or 2-h post-load glucose ≥ 11.1 mmol/litre<br><u>IGT:</u> FBG < 7.0mmol/litre and 2h glucose of 7.8-11.0 mmol/litre</td>
<td>
<table>
<tr><td></td><td colspan="3">Discharge OGTT</td><td></td></tr>
<tr><td>Admission</td><td>Diabetes</td><td>IGT</td><td>NGT</td><td>Total</td></tr>
<tr><td>no/mild (group 1)</td><td>15 (19%)</td><td>39 (48%)</td><td>27 (33%)</td><td>81</td></tr>
<tr><td>moderate (group 2)</td><td>21 (25%)</td><td>31 (37%)</td><td>31 (37%)</td><td>83</td></tr>
<tr><td>severe (group 3)</td><td>17 (47%)</td><td>8 (22%)</td><td>11 (31%)</td><td>36</td></tr>
<tr><td>P-value</td><td>0.002</td><td>0.008</td><td>n.s</td><td>200</td></tr>
</table>
OGTT identified diabetes in 53 patients (27%), IGT in 78 patients (39%) and normal glucose tolerance in 69 (35%) patients. When the fasting glucose criteria were applied, however, only 14 patients (7%) were diagnosed as having diabetes.<br>There was no significant difference in admission glucose between patients with normal glucose tolerance and patients with abnormal glucose tolerance (8.9±2.4 vs. 8.9±2.4, p = 0.93).<br><u>Predictors of abnormal glucose tolerance at discharge</u><br>Multivariate analysis showed that fasting glucose (OR 5.00, CI 1.97-12.50, P < 0.001) and $Hb_{A1c}$ (OR 5.76, CI 1.50-22.16, P = 0.01) were independent predictors of abnormal glucose tolerance, but admission glucose was not (OR 0.98, CI 0.84-1.16, P = 0.85). Other significant predictors include fasting insulin (OR 1.17, CI 1.04-1.31, P = 0.007)
</td>
<td>at admission and one week after (discharge)</td>
<td>this study</td>
<td>admission hyperglycaemia in non-diabetic patients with AMI does not represent previously undiagnosed abnormal glucose tolerance. Fasting glucose and $Hb_{A1c,}$ rather than admission glucose, may be useful to predict abnormal glucose tolerance</td>
</tr>
</table>

| Bibliography (Ref ID) | Study type/aim | Number of patients and characteristics | Definitions and outcome measures | Risk factors/results | Length of follow-up | Source of funding | Additional comments |
|---|---|---|---|---|---|---|---|
| | | diabetes, those who died during hospitalisation and those who underwent coronary bypass surgery. The mean admission glucose concentration was 8.9 mmol/litre. There were 81 patients in group 1, 83 in group 2 and 36 in group 3.There were no significant differences in baseline characteristics , except lower prevalence of prior MI, | **NGT:** FBG < 7.0 mmol/litre and 2h glucose < 7.8 mmol/litre<br>The values of 7.8mmol/litre and 11.1mmol/litre were also used for classification of admission hyperglycaemia.<br>**Abnormal glucose tolerance**: was used to describe the presence of newly diagnosed diabetes or IGT.<br>**AMI:** diagnosed by chest pain consistent with ongoing myocardial ischaemia persisting longer than 30 mins and concomitant electrocardiographic changes. | and time to angiography (OR 1.17, CI 1.04-1.32, P = 0.01).<br>ROC curves assessing the ability of baseline variables to detect newly diagnosed diabetes showed area under the curve (AUC) for fasting glucose of 0.90 (P < 0.001), 0.85 for $Hb_{A1c}$ (P < 0.001) and 0.65 for admission glucose (P = 0.003).<br>ROC curves assessing the ability of baseline variables to detect abnormal glucose tolerance showed AUC of 0.76 for fasting glucose (P < 0.001) and 0.71 for $Hb_{A1c}$ (P < 0.001), but it was 0.50 for admission glucose (P = 0.93). | | | |

<table>
<tr><th>Bibliography (Ref ID)</th><th>Study type/aim</th><th>Number of patients and characteristics</th><th>Definitions and outcome measures</th><th>Risk factors/results</th><th>Length of follow-up</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td>higher Killip class and higher $HbA_{1c}$ in patients with higher admission glucose levels.</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Norhammar et al 2002 (1020)</td><td>To ascertain the prevalence of impaired glucose metabolism in patients without diagnosed diabetes but with MI and to assess whether such abnormalities can be identified in the early course of an MI.</td><td>144 patients (181 initially but only 144 tested at discharge and 3 months later) with suspected AMI with baseline blood glucose < 11.1mmol/litre. Patients had a mean age 63.5 years, 68% were male and mean blood glucose at admission</td><td>Blood glucose was analysed as soon as possible after admission. An OGTT was taken at discharge (day 4 or 5). 3 months after discharge, FBG and a new OGTT after 12h fasting was carried out. Definitions for diabetes and IGT were taken from WHO 1998 classification and the fasting blood glucose criteria was adopted from</td><td><u>Mean blood glucose</u><br>Mean blood glucose at admission was 6.5mmol/litre, mean 2-h postload blood glucose OGTT was 9.2mmol/litre at discharge (day 4 or 5) and 9.0mmol/litre 3 months later.<br><u>Multiple logistic regression of independent predictors of diabetes and abnormal glucose tolerance 3 months after discharge</u>
<table>
<tr><td></td><td colspan="2">Diabetes</td><td colspan="2">IGT and diabetes</td></tr>
<tr><td>Parameter</td><td>Odds Ratio (CI)</td><td>P</td><td>Odds Ratio (CI)</td><td>P</td></tr>
<tr><td>Previous hypertension</td><td>0.53 (0.29-0.91)</td><td>0.03</td><td>0.88 (0.56-1.37)</td><td>0.57</td></tr>
<tr><td>BMI (for increase of 1kg/$m^2$ )</td><td>1.13 (1.01-1.29)</td><td>0.04</td><td>1.06 (0.96-1.17)</td><td>0.26</td></tr>
<tr><td>$HbA_{1c}$ (for increase in 1%)</td><td>2.32 (1.11-5.18)</td><td>0.03</td><td>2.55 (1.23-5.64)</td><td>0.02</td></tr>
</table>
<u>Predictors of diagnosis at 3 months:</u></td><td>Patients were tested before hospital discharge and 3 months later.</td><td>Swedish Heart and Lung Foundation and Aventis Pharmaceuticals</td><td>Authors conclude that fasting and postchallenge hyperglycaemia in the early phase of AMI could be used as early markers of high-risk individuals.</td></tr>
</table>

<table>
<tr><th>Bibliography (Ref ID)</th><th>Study type/aim</th><th>Number of patients and characteristics</th><th>Definitions and outcome measures</th><th>Risk factors/results</th><th>Length of follow-up</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td>was 6.5mmol/litre.<br><u>Exclusion:</u> patients with known diabetes and aged > 80 years or serum creatinine concentration of 200µmol/litre</td><td>the ADA 1997<br><u>Diabetes:</u> fasting blood glucose > 6.0mmol/litre or 2 hour postload blood glucose > 11.0mmol/litre or both.<br><u>Impaired glucose tolerance:</u> fasting blood glucose < 6.1mmol/litre and 2 hour blood glucose 7.8-11.0 mmol/litre<br><u>Normal glucose tolerance:</u> fasting blood glucose < 6.1mmol/litre and 2 hour blood glucose < 7.8mmol/litre<br><u>AMI:</u> defined as European Society of Cardiology and the American</td><td>The area under the curve was 0.710 (P < 0.0001) for fasting blood glucose and 0.685 (P = 0.001) for $HbA_{1c.}$ A fasting glucose of > 5.3mmol/litre on day 4 (discharge) was able to predict newly detected diabetes at 3 months with a sensitivity of 80% and a specificity of 57%. The corresponding sensitivity and specificity values for $HbA_{1c}$ of more than 4.9% were 79% and 49%. When entering fasting blood glucose concentration on day 4 in the analysis, this parameter was the only remaining independent predictor of diabetes.<br><u>Multiple logistic regression of independent predictors of diabetes and abnormal glucose tolerance 3 months after discharge</u>
<table>
<tr><td></td><td colspan="2">Diabetes</td><td colspan="2">IGT and diabetes</td></tr>
<tr><td>Parameter</td><td>Odds Ratio (CI)</td><td>P</td><td>Odds Ratio (CI)</td><td>P</td></tr>
<tr><td>FBG day 4 (for increase in 1mmol/litre in blood glucose</td><td>2.97 (1.55-6.40)</td><td>0.002</td><td>1.90 (1.05-3.69)</td><td>0.04</td></tr>
<tr><td>$HbA_{1c}$ (for increase in 1%)</td><td>1.73 (0.72-4.31)</td><td>0.220</td><td>2.58 (1.17-6.09)</td><td>0.02</td></tr>
</table>
Since some patients were discharged on day 4 rather than day 5, the FBG obtained on this day was used in analyses. Inclusion of the fasting blood glucose on day 4 in the model rendered both</td><td></td><td></td><td></td></tr>
</table>

<table>
<tr><th>Bibliography (Ref ID)</th><th>Study type/aim</th><th>Number of patients and characteristics</th><th>Definitions and outcome measures</th><th>Risk factors/results</th><th>Length of follow-up</th><th>Source of funding</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td>College of Cardiology.</td><td>$HbA_{1c}$ and fasting blood glucose as independent predictors of abnormal glucose tolerance.</td><td></td><td></td><td></td></tr>
<tr><td>Okosieme et al 2008 (1329)</td><td>To clarify the prevalence of unrecognised abnormal glucose tolerance in population of patients with ACS in South Wales, UK and to analyse the performance of fasting and admission glucose (applied individually or in combination) as markers of previously undiagnosed diabetes in patients with ACS.</td><td>140 patients admitted to coronary care unit with diagnosis of ACS. There were no significant differences between in age, sex and ethnic distribution between the various categories of glucose tolerance.<br><u>Exclusion:</u> patients with previously known diabetes or IGT.</td><td>Casual blood glucose was taken on the day of admission (when one admission glucose level was available the highest reading was selected for analysis). An OGTT was performed before discharge (usually between day 5 and 7). Glycaemic status was classified on basis of 2-h postload (2-h plasma glucose) glucose values of the OGTT according to WHO 1998 definition and FPG on the basis</td><td><u>Prevalence of abnormal glucose tolerance at discharge</u><br>The prevalence of diabetes and IGT on the basis of OGTT were 27% and 39% respectively<br><u>Diagnostic accuracy of APG and FPG to diagnose diabetes in patients with ACS at discharge</u>
<table>
<tr><th></th><th>Prevalence</th><th>Sensitivity</th><th>Specificity</th><th>PPV</th></tr>
<tr><td>FPG ≥ 5.6 mmol/litre</td><td>48</td><td>81.6%</td><td>64.7 %</td><td>46.3%</td></tr>
<tr><td>APG ≥ 7.8 mmol/litre</td><td>30</td><td>65.8%</td><td>83.3 %</td><td>59.5%</td></tr>
<tr><td>FPG ≥ 5.6 or APG ≥ 7.8 mmol/litre</td><td>52</td><td>89.5%</td><td>56.9 %</td><td>43.6%</td></tr>
</table>
The AUCs for diagnosing diabetes were 0.83 (P < 0.001) for FPG, 0.79 (P < 0.001) for APG and 0.84 (P < 0.001) for FPG and APG applied in combination. The optimal cut-off point for diagnosing diabetes with FPG was 5.8mmol/litre. This is the FBG value with the best sensitivity and</td><td>Blood glucose was measured on admission and OGTT before discharge (usually days 5 and 7)</td><td>Not reported.</td><td>The authors conclude that the combination of FPG ≥ 5.6mmol/litre and/or APG ≥ 7.8mmol/litre was highly sensitive for identifying diabetes. Although weakly specific, this simple algorithm could offer a practical initial screening tool at the acute setting in the high risk population with ACS.</td></tr>
</table>

| Bibliography (Ref ID) | Study type/aim | Number of patients and characteristics | Definitions and outcome measures | Risk factors/results | Length of follow-up | Source of funding | Additional comments |
|---|---|---|---|---|---|---|---|
| | | | of American Diabetes Association 2004 criteria: **Normal Glucose Tolerance:** 2-h plasma glucose < 7.8mmol/litre or FPG < 5.6mmol/litre **Impaired Glucose Tolerance:** 2-h plasma glucose 7.8-11.0mmol/litre or **Impaired Fasting Glucose:** FPG 5.6-6.9mmol/litre **Diabetes:** 2-h plasma glucose ≥ 11.1mmol/litre or FPG > 7.0mmol/litre **Admission Plasma Glucose (APG)** was stratified into 3 | specificity for identifying diabetes in this setup. At this cut-off the sensitivity and specificity of FPG in detecting diabetes were 69.2 and 77.2% respectively. The optimal cut-off point for identifying diabetes with APG was 7.7mmol/litre; this cut-off point was associated with sensitivity of 65.8% and specificity of 82.4%. | | | |

| Bibliography (Ref ID) | Study type/aim | Number of patients and characteristics | Definitions and outcome measures | Risk factors/results | Length of follow-up | Source of funding | Additional comments |
|---|---|---|---|---|---|---|---|
| | | | groups: < 7.8mmol/litre, 7.8-11.0mmol/litre and ≥ 11.1mmol/litre.<br>**AMI:** diagnosis based on joint recommendations by European Society of Cardiology and American College of Cardiology. | | | | |
| Oswald & Yudkin 1987 (Ref ID: | Clinical audit (prognostic design)/ to investigate validated levels of $HbA_{1c}$ indicative of diabetes in order to assess the contribution of undiagnosed diabetes to admission | 397 patients with confirmed AMI (463 initially but 66 had known diabetes and were excluded). In 248 patients an admission plasma glucose level was estimated before administration | Categorisation of $HbA_{1c}$<br>**Clearly normal (group 1):** < 6.9%<br>**Borderline (group 2):** 6.9-7.8%<br>**Clearly abnormal $HbA_{1c}$ (group 3):** > 7.8%<br>Diabetes and IGT were defined according to the | **$HbA_{1c}$**<br>A level of $HbA_{1c}$ > 7.8% (classified as clearly abnormal) was 100% sensitive and 99% (CI 97-100%) specific for overt diabetes, but when all diabetes at follow-up was included, the sensitivity fell to 67% (CI 36-97%) with the same specificity. IGT was more common in group 2 than group 1 ($p < 0.001$).<br>**Admission plasma glucose (APG)**<br>APG was detailed in 248 patients before administration of glucose. The level was ≥ 11mmol/litre in 49 (20%) of these patients. Sensitivity for DM was 33% (CI 3-64%), specificity for DM was 91% (CI 85-97%). For overt diabetes the sensitivity is 50% (CI 9 to 91%) and specificity | 293/397 patients survived. 117 patients had an OGTT at 7-10 days (before discharge). 61 of these patients went on | | In four patients with fasting plasma glucose < 8mmol/litre but with 2h plasma glucose ≥ 11mmol/litre at 3 months follow-up, the OGTT was repeated at 6 months from |

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|---|---|---|---|---|---|---|---|
| | hyperglycaemia after AMI | of glucose solution. There were no significant difference between patients sampled for plasma glucose and those not sampled in terms in gender, age or outcome. OGTT was carried out in 117/293 survivors between 7-10 days after infarction and before discharge. | WHO criteria using venous plasma. 2 elevated glucose values were required in the absence of symptoms. | 91% (CI 85 to 97%). | to have an OGTT at 3 months and 49 randomly selected patients had their first OGTT at 3 months so a total of 110 had a follow-up at 3 months. | | AMI. Paper does not report specific definitions of overt diabetes and diabetes but assumption that overt diabetes refers to symptomatic diabetes. |

### *Review question 4: What information should patients with peri ACS and hyperglycaemia (who are at high risk of developing diabetes) be provided while waiting for a referral for diagnostic investigations for diabetes?*

No studies were identified for this question.