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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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:

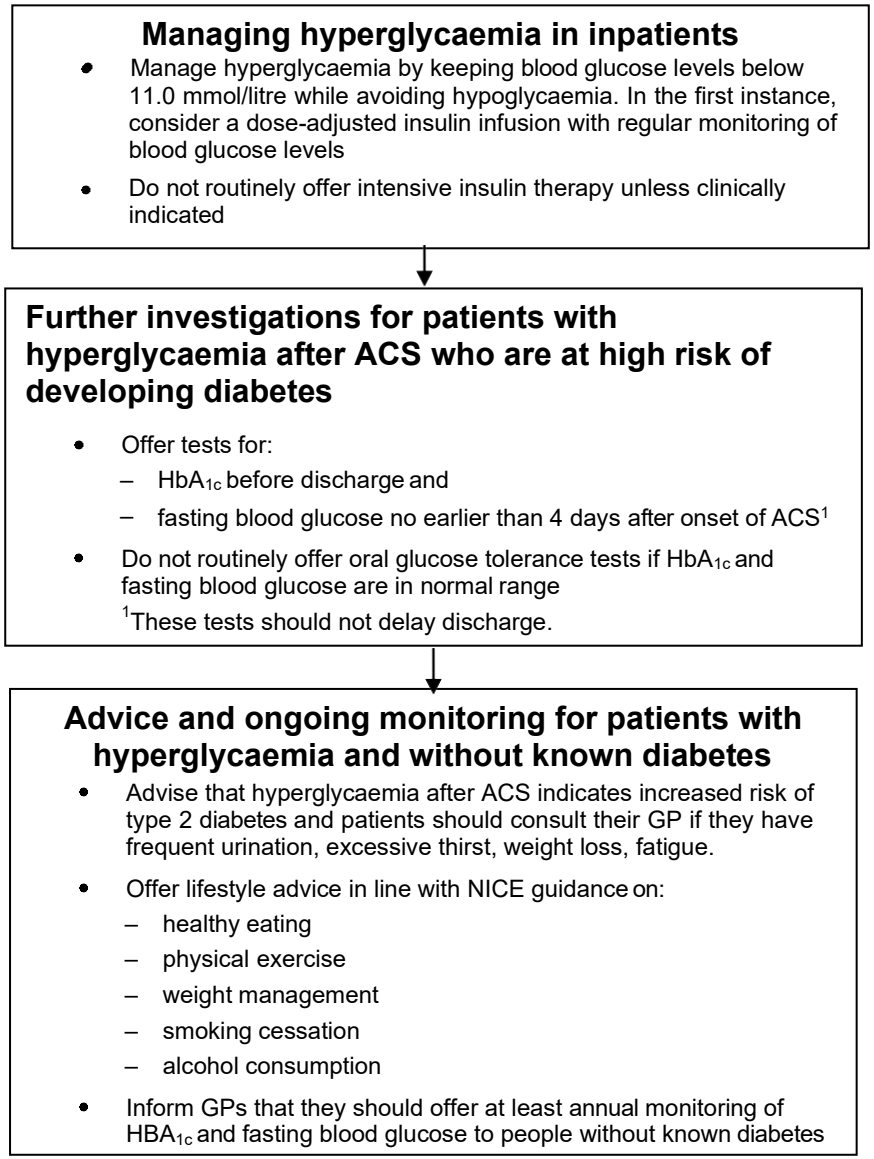
- healthy eating in line with 'MI: secondary prevention' (NICE clinical guideline 48) and 'Obesity' (NICE clinical guideline 43)
- physical exercise in line with 'MI: secondary prevention' (NICE clinical guideline 48) and 'Four commonly used methods to increase physical activity' (NICE public health 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) 3-month mortality (adj OR 4.7, 95% CI 1.0 to 22.4, p = 0.05) 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) No previous insulin and high risk (RR 0.85, 95% CI 0.50 to 1.45, p = 0.55) Previous insulin and low risk (RR 0.86, 95% CI 0.42 to 1.78, p = 0.68) 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) No previous insulin and high risk (RR 1.02, 95% CI 0.74 to 1.40, p = 0.91) Previous insulin and low risk (RR 0.74, 95% CI 0.45 to 1.23 p = 0.25) 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. [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) NSTEMI (57/359)	STEMI (193/755) 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 Diabetes: FBG ≥ 6.1 mmol/litre and/or BG-2h ≥ 11.1 mmol/litre 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 Diabetes: FBG > 6.0 mmol/litre and/or BG-2h > 11.0 mmol/litre 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 Diabetes: FBG ≥ 7.0 mmol/litre and/or BG-2h ≥ 11.1 mmol/litre 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 Diabetes: BG-2h ≥ 11.1 mmol/litre, FPG ≥ 7.0 mmol/litre 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: • 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) • fasting insulin (OR 1.17, 95% CI 1.04 to 1.31, p = 0.007) • 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: sensitivity values were 72% (95% CI 58 to 83%) and 66% (95% CI 49 to 80%) specificity values were 45% (95% CI 37 to 53%) and 83% (95% CI 75 to 90%) 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%)	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: 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]: 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: 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) 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) 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 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

Cheung NW, Wong VW, McLean M (2006) The hyperglycemia: intensive insulin infusion in infarction (HI-5) study: a randomized controlled trial of insulin infusion therapy for myocardial infarction. Diabetes Care 29: 765–70

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

Malmberg K, Rydén L, Efendic S et al. (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: 57–65

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

Weston C, Walker L, Birkhead J (2007) Early impact of insulin treatment on mortality for hyperglycaemic patients without known diabetes who present with an acute coronary syndrome. Heart 93: 1542–7

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

The Guideline Development Group

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The Guideline Review Panel

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
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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.