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

NICE clinical guideline

Draft for consultation, May 2011

This guideline was developed following the NICE short clinical guideline process. This document includes all the recommendations, details of how they were developed and summaries of the evidence they were based on.

Contents

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

Introduction

Management of hyperglycaemia in acute coronary syndromes

Acute coronary syndromes (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 (heart attack) 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.

This guideline covers the glucometabolic management of hyperglycaemia within the first 48 hours in people admitted to hospital for ACS. The guideline focuses on intensive insulin therapy, which usually consists of an infusion of either glucose and insulin or glucose, insulin and potassium. For the purposes of this guideline, hyperglycaemia is defined as a blood glucose level usually above 11 mmol/litre.

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.

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/consent) and the code of practice that accompanies the Mental Capacity Act (summary available from www.publicguardian.gov.uk). In Wales, healthcare professionals should follow advice on consent from the Welsh Assembly 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

1.1.1 Do not routinely offer intensive insulin therapy to manage hyperglycaemia in patients admitted to hospital for an acute coronary syndrome (ACS).

1.1.2 Manage acute hyperglycaemia (blood glucose above 11.0 mmol/litre) in accordance with local guidelines.

1.1.3 Offer patients 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 patients without known diabetes oral glucose tolerance tests if HbA_{1c} and fasting blood glucose levels are within the normal range.

1.1.5 Offer patients 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

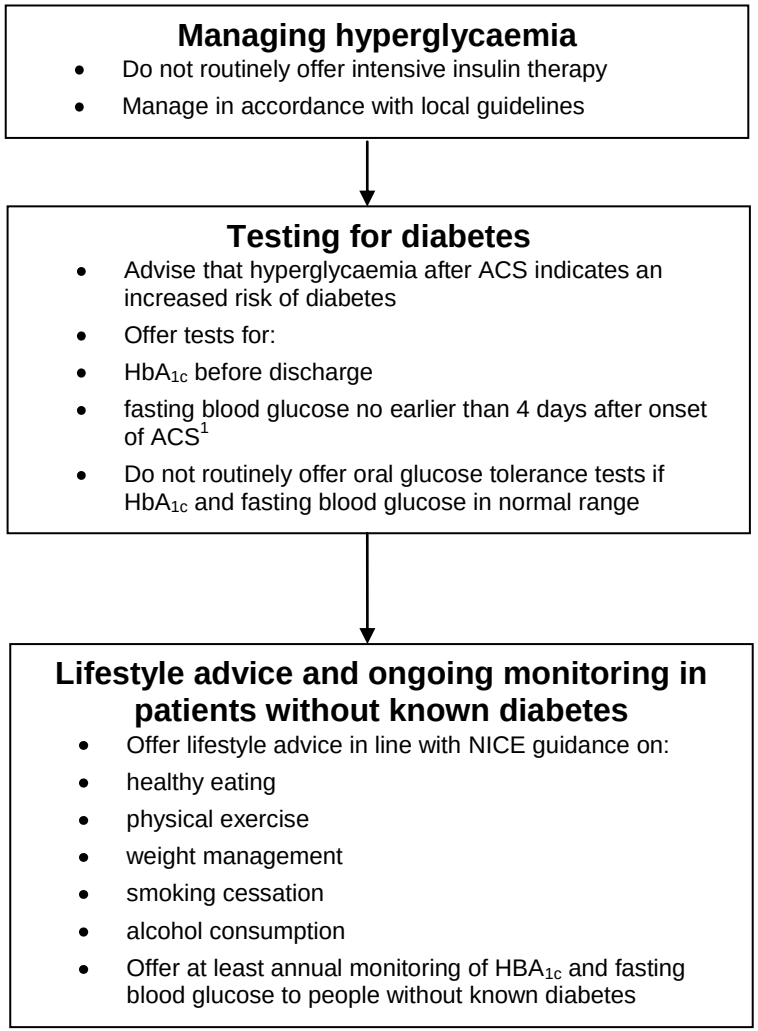
clinical guideline 48) and ‘Brief interventions and referral for smoking cessation’ (NICE public health guidance 1)

- alcohol consumption in line with ‘Alcohol dependence and harmful alcohol use’ (NICE clinical guideline 115), ‘Alcohol-use disorders – preventing harmful drinking’ (NICE public health guidance 24), and ‘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 diabetes.

1.1.7 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



[1]These tests should not delay discharge.

3 Evidence review and recommendations

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

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

Ten papers were selected for this review question. The papers were based on four primary studies (Cheung et al. 2006; Malmberg et al. 1995; Malmberg et al. 2005; CREATE-ECLA 2005), all of which were randomised controlled trials (RCTs) comparing an intensive insulin intervention with standard therapy in patients with ACS and hyperglycaemia. 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).

A meta-analysis was 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).

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	Definition of hyperglycaemia	Treatment	Location	Outcomes reported for patients with diabetes
Malmberg et al. 1995 (DIGAMI 1)	Mean 3.4 years	Diabetes and blood glucose level > 11 mmol/litre or blood glucose level > 11 mmol/litre and no diabetes	Glucose–insulin infusion and subcutaneous insulin	Sweden	Mortality, reinfarction, heart failure and hypoglycaemia
Malmberg et al. 2005 (DIGAMI 2)	Mean 3.4 years	Blood glucose level > 11 mmol/litre or type 2 diabetes	Glucose–insulin infusion with insulin-based long-term glucose control	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	Blood glucose level > 7.8 mmol/litre	Glucose–insulin infusion	Australia	Mortality, reinfarction and heart failure
CREATE-ECLA 2005	30 days	Mean glucose levels 9.0 mmol/litre in both groups at baseline	Glucose–insulin-Potassium infusion	470 centres worldwide	Mortality

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)											
4 (Malmberg et al. 1995, Malmberg et al. 2005, Cheung et al. 2006, CREATE ECLA 2005)	Randomised trial	No serious limitations[g]	Serious[a]	Serious[b]	Serious[c]	None	472/2686 (17.6%)	440/2536 (17.4%)	1.02 (0.78 to 1.32)		VERY LOW
Inpatient mortality (follow-up median 10 days)											
2 (Malmberg et al. 1995, Cheung et al. 2006)	Randomised trial	No serious limitations[g]	Serious[a]	No serious indirectness	Serious[c]	None	34/432 (7.9%)	39/428 (9.1%)	0.87 (0.56 to 1.36)		LOW
3-month mortality (follow-up of up to 3 months)											
2 (Malmberg et al. 1995, Cheung et al. 2006)	Randomised trial	No serious limitations[g]	Serious[a]	No serious indirectness	Serious [c]	None	47/432 (10.9%)	51/428 (11.9%)	0.95 (0.52 to 1.76)		LOW
Reinfarction (follow-up median 2 years)											
3 (Malmberg et al. 1995, Malmberg et al. 2005, Cheung et al. 2006)	Randomised trial	No serious limitations[g]	Serious [a]	No serious indirectness	Serious [c]	None	79/844 (9.4%)	69/672 (10.2%)	1.19 (0.7 to 2.04)		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
Heart failure (follow-up of up to 10 days)											
2 (Malmberg et al. 1995, Cheung et al. 2006)	Randomised trial	No serious limitations[g]	Serious[a]	No serious indirectness	Serious [c]	None	169/432 (39.1%)	177/428 (41.3%)	0.81 (0.44 to 1.49)		LOW
Hypoglycaemia[d] (follow-up mean 24 hours)											
2 (Malmberg et al. 1995, Malmberg et al. 2005)	Randomised trial	No serious limitations[g]	Serious[a]	No serious indirectness	Serious[c]	None	106/780 (13.6%)	4/621 (0.006%)	19.32 (5.79 to 64.41)		LOW
Measure of blood glucose (follow-up mean 24 hours)											
2 (Malmberg et al. 1995, Malmberg et al. 2005)	Randomised trial	No serious limitations[g]	Serious[a]	No serious indirectness	Serious[c]	None	780	620	-	−1.49 (−2.66 to −0.31)	LOW
Subgroup analyses of mortality by mean blood glucose level < 8 mmol/litre and > 8 mmol/litre in the first 24 hours[e]											
1 (Cheung et al. 2006)	Randomised trial	No serious limitations[g]	Serious[a]	No serious indirectness	Serious[c]	None	Inpatient mortality (adj OR 7.2, 95% CI 0.9 to 58.9) 3 month mortality (adj OR 4.7, 95% CI 1.0 to 22.4) 6 month mortality (adj OR 5.6, 95% CI 1.2 to 26.1)				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
Subgroup analyses of 1 year mortality stratified by risk[f]											
1 (Malmberg et al. 1995)	Randomised trial	No serious limitations[g]	Serious[a]	No serious indirectness	Serious[c]	None	No previous insulin and low risk (RR 0.48, CI 0.25 to 0.92) No previous insulin and high risk (RR 0.85, CI 0.50 to 1.45) Previous insulin and low risk (RR 0.86, CI 0.42 to 1.78) Previous insulin and high risk (RR 0.78, CI 0.49 to 1.26)				LOW
Subgroup analyses of mortality up to 3.4 years stratified by risk[f]											
1 (Malberg et al. 1995)	Randomised trial	No serious limitations[g]	Serious[a]	No serious indirectness	Serious[c]	None	No previous insulin and low risk (RR 0.54, CI 0.35 to 0.84) No previous insulin and high risk (RR 1.02, CI 0.74 to 1.40) Previous insulin and low risk (RR 0.74, CI 0.45 to 1.23) Previous insulin and high risk (RR 0.82, CI 0.59 to 1.13)				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

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

[b] Patients in the CREATE-ECLA study were given GIK (glucose, insulin and potassium) infusion; patients in both DIGAMI studies (Malmberg et al. 1995 and Malmberg et al. 2005) were given GI (glucose and insulin) infusion.

[c] Wide confidence intervals.

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

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

[f] 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.

[g] 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.

Abbreviations: adj, adjusted for age, gender and cardiac intervention (PTCA or thrombolysis); 95% CI, 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 5222 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 (relative risk [RR] 1.02, 95% confidence interval [95% CI] 0.78 to 1.32).*

3.1.3.2 *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 *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 *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 *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 *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 *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 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 Low-quality evidence from one study with 272 patients showed that intensive insulin therapy 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 Low-quality evidence from one study with 272 patients showed that intensive insulin therapy 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 Guideline Development Group (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 intensive insulin therapy is clearly more expensive and less effective 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 £85.75. Table 3 below provides an estimate of resource use and unit costs of managing hyperglycaemia using intensive insulin therapy compared with standard care.

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
IV 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)	0.62	(0.62 to 3.00)	14.88	0.00	CADTH CAD converted
IV 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
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, 60 minutes: blood glucose test (5 min/test x 4 additional tests per 24 hours = 20 min/24 hours; 40 min/hospital stay), infusion bag preparation (10 min per bag x 2 = 20 min)	33 (gross pay Band 6 nurse)	(22 to 60)	33	0.00	PSSRU (2010)

Estimated cost per hospital stay (48 hours)			127.24	41.46	
Incremental cost			£85.78		

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 a non-significant effect on overall mortality, although the DIGAMI 1 study showed a 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 to when the study was conducted in 1995, particularly with regard to anti-platelet therapy, statin therapy and coronary revascularization 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. The group also noted that the initial findings of DIGAMI 1 were not replicated in the DIGAMI 2 study conducted in 2005, the CREATE-ECLA study or the HI-5 study (Cheung et al. 2006). The GDG did, however, recognise that the DIGAMI 2 study was underpowered, did not reach the pre-specified glucose endpoints and there was not an adequate separation of the 3 groups in terms of blood glucose levels. The GDG also recognised that the GIK infusion used in the CREATE-ECLA study resulted in an initial rise in mean blood glucose concentration in the intervention group (after 6 hours). 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. They recognised that the risk of adverse events associated with uncontrolled hyperglycaemia were high and it was felt a separate recommendation should be made to ensure that hyperglycaemia is managed.

.

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

Recommendations

Recommendation 1.1.1

Do not routinely offer intensive insulin therapy to manage hyperglycaemia in patients admitted to hospital for an acute coronary syndrome (ACS).

Recommendation 1.1.2

Manage acute hyperglycaemia (blood glucose above 11.0 mmol/litre) in accordance with local guidelines.

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 known or unknown 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

Four studies were selected for this review question, three papers (Cheung et al. 2006; van der Horst et al. 2003; CREATE-ECLA 2005) were RCTs comparing an intensive insulin intervention with standard therapy in patients with ACS and hyperglycaemia. The remaining one (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 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).

A meta-analysis was carried out for various outcomes, including mortality at different time points, rates of heart failure, reinfarction and any composite end point, which included death, recurrent infarction or repeat angioplasty (see appendix E for full forest plots)

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

Author/study	Follow-up	Definition of hyperglycaemia	Treatment	Location	Outcomes reported for patients without diabetes
Weston et al. 2007 (MINAP)	None past the inpatient stay	≥ 11 mmol/litre	Intensive glucose-insulin given to approximately 70% of patients, 26% of patients were given insulin pump and 5% a single dose	UK	Mortality at 7 and 30 days
Cheung et al. 2006 (HI-5)	6 months	≥ 7.8 mmol/litre	Glucose-insulin infusion	Australia	Heart failure and reinfarction
Van der Horst et al. 2003	30 days	Median blood glucose 8.5 mmol/litre in both groups	Glucose-insulin-potassium infusion	The Netherlands	30 day mortality, reinfarction and adverse events
CREATE-ECLA 2005	30 days	Mean blood glucose of 9.0 mmol/litre in both groups at baseline	Glucose-insulin-potassium infusion	470 centres worldwide	30 day mortality, heart failure and hypoglycaemia

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											
2 (Van der Horst et al. 2003, CREATE-ECLA 2005)	Randomised trial	No serious limitations[c]	Serious[d]	Serious[e]	No serious imprecision	None	773/8684 (8.9%)	750/8661 (8.7%)	1.03 (0.93 to 1.13)	0 fewer per 100 (from 1 fewer to1 more)	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
Heart failure after up to 7 days											
2(Cheung et al. 2006, CREATE-ECLA 2005)	Randomised trial	No serious limitations[c]	Serious[d]	Serious[f]	Very serious[g]	None	1728/ 10150 (17.0%)	1728/10169 (17.0%)	0.71 (0.30 to 1.67)	5 fewer per 100 (from 12 fewer to 11 more)	VERY LOW
Reinfarction (follow-up of up to 3 months)											
2 (Cheung et al. 2006, Van der Horst et al. 2003)	Randomised 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		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	intensive insulin	standard therapy	Relative risk (95% CI)	Absolute	
Composite endpoint[j] (follow-up mean 30 days)											
1 (Van der Horst et al. 2003)	Randomised 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 (Weston et al. 2007)	Observational study	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	841	1682	Rates of hypoglycaemia were not reported		VERY LOW
2 (Van der Horst et al. 2003, CREATE-ECLA 2005)	Randomised trial	No serious limitations[c]	Serious[d]	Serious[i,f]	No serious imprecision	None	34/8617 (0.39%)	11/8621 (0.13%)	Symptomatic hypoglycaemia was significantly increased in patients given intensive insulin treatment (HR 3.11, CI 1.57 to 6.13)		LOW
Subgroup analyses of overall mortality, 7-day mortality, reinfarction and composite end points											
1 (Van der Horst et al. 2003)	Randomised trial	No serious limitations[c]	Serious[d]	Serious[i]	Serious[b]	None	30 day mortality (RR 0.36, CI 0.13 to 0.99) was significantly reduced in patients with Killip class 1 compared with patients with Killip class 2 (RR 0.31, CI 0.03 to 3.08), Killip class 3 (RR 2.14, CI 0.73 to 6.28) and Killip class 4 (RR 1.45, CI 0.51 to 4.13). Composite end-point (adjusted RR 0.47[k], CI 0.27 to 0.83) was also significantly reduced in patients with Killip class 1. Reinfarction was non-significantly reduced in patients with Killip class 1 (adjusted RR 0.39[k], CI 0.09 to 1.63)				VERY LOW
1 (CREATE-ECLA 2005)	Randomised trial	No serious limitations[c]	Serious[d]	Serious[f]	Serious[b]	None	30 day mortality was significantly increased in patients given intensive insulin treatment with a baseline blood glucose level < 7 mmol/litre (RR 1.24, CI 1.05 to 1.48). Mortality was non-significantly affected by intensive insulin treatment in patients with a baseline blood glucose level 7 to < 8 mmol/litre (RR 0.87, CI 0.75 to 1.02) and > 8 mmol/litre (RR 1.02, CI 0.90 to 1.15)				VERY LOW

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 (Weston et al. 2007)	Observational study	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	30 day mortality was significantly reduced in patients with STEMI (RR 0.61, CI 0.49 to 0.78) compared with patients with NSTEMI (RR 0.81, CI 0.62 to 1.07) and this was also true at 7 days (RR 0.61, CI 0.47 to 0.79).				VERY LOW

[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] 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.

[f] The CREATE-ECLA study included patients with diabetes for this outcome (approx 18%).

[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).

[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 (approx 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. CREATE-ECLA reported data from India, China and Pakistan only.

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: CI, 95% confidence interval; HR, hazard ratio; RR, relative risk.

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 *Low quality evidence from two RCTs of 17345 patients without previous diabetes showed that intensive insulin non-significantly increased 30 day mortality compared with standard care (RR 1.03, 95% CI 0.93 to 1.13).*

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 two RCTs of 20319 patients showed a non-significant reduction in inpatient heart failure in patients given intensive insulin compared with those given standard therapy (RR 0.71, 95% CI 0.30 to 1.67).*

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 Very low quality evidence from one observational study of 2523 patients did not report rates of hypoglycaemia.

3.2.3.8 Low quality evidence from two RCTs of 21036 patients showed that symptomatic hypoglycaemia was significantly increased in patients given intensive insulin treatment (HR 3.11, 95% CI 1.57 to 6.13).

3.2.3.9 Very low quality evidence from one RCT of 841 patients showed that 30 day mortality (RR 0.36, CI 0.13 to 0.99) and composite end-point (RR 0.50, 95% CI 0.29 to 0.87) were significantly reduced in patients with Killip class 1 (see glossary) compared with patients with class 2 (RR 0.31, 95% CI 0.03 to 3.08), class 3 (RR 2.14, 95% CI 0.73 to 6.28) and class 4 (RR 1.45, 95% CI 0.51 to 4.13). Reinfarction was non-significantly reduced in patients with Killip class 1 (RR 0.50, 95% CI 0.13 to 2.00).

3.2.3.10 Very low quality evidence from one RCT of 20195 patients showed that 30 day mortality was significantly increased in patients given intensive insulin treatment with a baseline blood glucose below 7 mmol/litre (RR 1.24, 95% CI 1.05 to 1.48). A non-significant effect on mortality was shown for patients given intensive insulin treatment with baseline blood glucose 7 to 8 mmol/litre (RR 0.87, 95% CI 0.75 to 1.02) and more than 8 mmol/litre (RR 1.02, 95% CI 0.90 to 1.15).

3.2.3.11 Very low quality evidence from one observational study of 2523 patients showed 30-day mortality was significantly reduced in patients with STEMI (RR 0.61, 95% CI 0.49 to 0.78) compared with patients with NSTEMI (RR 0.81, 95% CI 0.62 to 1.07) and this was also true at 7 days (RR 0.61, 95% CI 0.47 to 0.79).

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 in this case because intensive insulin therapy is evidently more costly than standard care, and at best equally effective. The incremental cost of using intensive insulin therapy to manage hyperglycaemia in patients with ACS without pre-existing diabetes was estimated to be £95.70 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 management of hyperglycaemia using intensive insulin therapy compared with standard care.

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
1litre 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
IV 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)	£0.62	(0.62 to 3.00)	24.80	0.00	CADTH CAD converted
IV 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 min/test x 4 additional tests per 24 hours = 20 min/24 hours; 40 min/inpatient stay), infusion bag preparation (10 min per bag x 2 = 20 min)	33 Gross pay Band 6 nurse	(22 to 60)	33	0.00	PSSRU (2010)
Estimated cost per hospital stay (48 hours)			96.66	0.96	
Incremental cost			£95.70		

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, it 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 RCTs conducted by Van der Horst and the CREATE-ECLA study 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 both the Van der Horst and CREATE-ECLA studies 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. They also recognised that the risk of adverse events associated with uncontrolled hyperglycaemia were high and it was felt a separate recommendation should be made to ensure that hyperglycaemia is managed.

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

Recommendations

Recommendation 1.1.1

Do not routinely offer intensive insulin therapy to manage hyperglycaemia in patients admitted to hospital for an acute coronary syndrome (ACS).

Recommendation 1.1.2

Manage acute hyperglycaemia (blood glucose above 11.0 mmol/litre) in accordance with local guidelines.

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 known or unknown 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

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 adapted 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	Location
Tenerz et al. (2003)	3 months	Capillary whole blood	Sweden
Norhammar et al. (2002)	3 months	Capillary whole blood	Sweden
Ishihara et al. (2006)	Discharge from hospital	Plasma glucose	Japan
Okosieme et al. (2008)	Discharge from hospital	Plasma glucose	UK
Oswald and Yudkin (1987)	At 7–10 days and at 3 months	Plasma glucose	UK

Table 8 GRADE table summary for risk factors associated with diabetes

Quality assessment							Summary of findings				
							No of patients				
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Total	Diabetes at follow-up	Effect/Outcome	Length of follow-up	Quality[a]
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	No serious imprecision	No serious other considerations	626	163	The prevalence of diabetes[c] 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[d]	No serious imprecision	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, CI 1.97 to 12.50, p < 0.001), HbA_{1c} (OR 5.76, CI 1.50-22.16, p = 0.01), • fasting insulin (OR 1.17, CI 1.04 to 1.31, p = 0.007), • time to angiography (OR 1.17, CI 1.04 to 1.32, p = 0.01)	Discharge (up to 1 week after admission)	LOW

Quality assessment							Summary of findings				
							No of patients				
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Total	Diabetes at follow-up	Effect/Outcome	Length of follow-up	Quality[a]
1 study (Ishihara et al. 2006)	Prognostic	Serious[b]	No serious inconsistency	Serious[d]	No serious imprecision	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, CI 0.84 to 1.16, p = 0.85)	Discharge (up to 1 week after admission)	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	No serious imprecision	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% and 66% specificity values were 45% and 83% PPV 32% and 60% NPV 81% and 87%	Discharge (up to 1 week after admission)	MODERATE
1 study (Okosieme et al. 2008)	Prognostic	Serious[b]	No serious inconsistency	No serious indirectness	No serious imprecision	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%, specificity = 65%, PPV = 47%, AUC = 0.83	Discharge (up to 1 week after admission)	MODERATE
1 study (Okosieme et al. 2008)	Prognostic	Serious[b]	No serious inconsistency	No serious indirectness	No serious imprecision	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: sensitivity = 90%, specificity = 57%, PPV = 44%, AUC = 0.84	Discharge (up to 1 week after admission)	MODERATE

Quality assessment							Summary of findings				
							No of patients				
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Total	Diabetes at follow-up	Effect/Outcome	Length of follow-up	Quality[a]
1 study Okosieme et al. 2008)	Prognostic	Serious[b]	No serious inconsistency	No serious indirectness	No serious imprecision	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%) to identify diabetes at discharge	Discharge (up to 1 week after admission)	MODERATE
1 study, Okosieme et al. 2008)	Prognostic	Serious[b]	No serious inconsistency	No serious indirectness	No serious imprecision	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%) to identify diabetes at discharge	Discharge (up to 1 week after admission)	MODERATE
Longer-term multivariate predictors of diabetes											
1 study (Norhammar et al. 2002)	Prognostic	No serious limitations	No serious inconsistency	Serious[e]	No serious imprecision	No serious other considerations	142	36	Fasting blood glucose on day 4 (OR 2.97, CI 1.55 to 6.40, p = 0.002) was the only significant predictor of diabetes 3 months after admission[f]	3 months	MODERATE

Quality assessment							Summary of findings				
							No of patients				
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Total	Diabetes at follow-up	Effect/Outcome	Length of follow-up	Quality[a]
Longer-term multivariate predictors of diabetes or impaired glucose tolerance											
2 studies (Tenerz et al. 2003, Norhammar et al. 2002)	Prognostic	No serious limitations	No serious inconsistency	Serious[d]	No serious imprecision	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, CI 1.16 to 1.64) Fasting blood glucose on day 4 (OR 1.90, CI 1.05 to 3.69, p = 0.04) HbA_{1c} (for increase in 1%) (OR 2.58, CI 1.17 to 6.09, p = 0.02)	3 months	MODERATE
Longer-term use of predictors to diagnose diabetes											
1 study (Norhammar et al. 2002)	Prognostic	No serious limitations	No serious inconsistency	Serious[g]	No serious imprecision	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%) and AUC value was 0.710 (p < 0.0001).	3 months	MODERATE
1 study (Oswald & Yudkin 1987)	Prognostic	Serious[h]	No serious inconsistency	Serious[g]	No serious other considerations	No serious imprecision	110	9	An admission plasma glucose > 11 mmol/litre was able to predict diabetes at 3 months with a sensitivity of 33% (CI 3 to 64%) and a specificity of 91% (CI 85 to 97%)	3 months	LOW

Quality assessment							Summary of findings				
							No of patients				
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Total	Diabetes at follow-up	Effect/Outcome	Length of follow-up	Quality[a]
1 study Oswald & Yudkin 1987	Prognostic	Serious[h]	No serious inconsistency	Serious[g]	No serious other considerations	No serious imprecision	110	9	A HbA_{1c} > 7.8% was able to predict diabetes at 3 months with a sensitivity of 67% (CI 36 to 97%) and a specificity of 99% (CI 97 to 100%)	3 months	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] Using either fasting blood glucose or 2-h glucose criteria to diagnose diabetes.

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

[e] [Footnote missing].

[f] 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; 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 25–27% after up to 3 months follow-up.*

3.3.3.2 *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 *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 *Moderate quality evidence from two studies of 340 patients showed that an admission glucose above 7.8 mmol/litre predicted diabetes at discharge (sensitivity 72 and 66%, specificity 45 and 83%, positive predictive value [PPV] 32 and 60%, negative predictive value [NPV] 81 and 87%).*

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

3.3.3.5 *Moderate 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%, specificity 65%, PPV 47%, AUC 0.83).*

This study was conducted in the UK.

3.3.3.6 *Moderate 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%, AUC 0.84).*

This study was conducted in the UK.

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

This study was conducted in the UK.

3.3.3.8 *Moderate 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 of 69%, specificity 77%) to predict diabetes at discharge.*

This study was conducted in the UK.

3.3.3.9 *Moderate quality evidence from one study of 142 patients showed that fasting blood glucose on day 4 was a significant predictor of diabetes 3 months after admission.*

This study was conducted in Sweden.

3.3.3.10 *Moderate 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) and HbA_{1c} (OR 2.58 for 1 mmol/litre increase, 95% CI 1.17 to 6.09) were all significant predictors of diabetes or impaired glucose tolerance at 3 month follow-up.*

These studies were both conducted in Sweden.

3.3.3.11 Moderate 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 AUC of 0.710.

This study was conducted in Sweden.

3.3.3.12 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 Low quality evidence from one study of 110 patients showed that a HbA1c 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 adapted 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 within practice. They also felt that the evidence implied that patients with low fasting glucose and/or low HbA_{1c} would be less likely to develop diabetes, so testing for diabetes using an oral glucose tolerance test would not be as important for this group of patients at this stage.

3.3.6 Recommendations and research recommendations for risk of diabetes

Recommendations

Recommendation 1.1.3

Offer patients 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 patients without known diabetes oral glucose tolerance tests 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

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 diagnosed with 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 rehab**	**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 rehab 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 rehab**	**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. It 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 routine follow-up would help to monitor this high risk group. Specifically, it felt that follow-up should include a biochemical test to ensure that diabetes status is assessed.

The GDG also discussed the fact that some ethnic groups may have a lower index of suspicion for diabetes while other groups, such as people of south Asian descent, may be genetically predisposed to developing diabetes. However, it was felt that 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 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 'Alcohol dependence and harmful alcohol use' (NICE clinical guideline 115), 'Alcohol-use disorders – preventing harmful drinking' (NICE public health guidance 24), and '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 an increased risk of developing diabetes.

Recommendation 1.1.7

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/CG[xxx])'. Note: these details will apply when the guideline is published.

6 Other versions of this guideline

6.1 Quick reference guide

A quick reference guide for healthcare professionals is available from www.nice.org.uk/guidance/CG[xxx]/QuickRefGuide

For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk (quote reference number N[xxxx]). Note: these details will apply when the guideline is published.

6.2 'Understanding NICE guidance'

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

For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk (quote reference number N[xxxx]). Note: these details will apply when the guideline is published.

We encourage NHS and voluntary sector organisations to use text from this booklet in their own information about [condition].

7 Related NICE guidance

Published

- 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
- 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
- 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 CG 94)
- 'Four commonly used methods to increase physical activity' (NICE public health guidance 2, 2006) Available from http://guidance.nice.org.uk/PH2
- 'Smoking cessation services' (NICE public health guidance 10, 2008), Available from http://guidance.nice.org.uk/PH10
- 'Brief interventions and referral for smoking cessation' (NICE public health guidance 1, 2006) Available from http://guidance.nice.org.uk/PH1
- 'Alcohol dependence and harmful alcohol use' (NICE clinical guideline 115, 2011) Available from www.nice.org.uk/guidance/CG115
- 'Alcohol-use disorders – preventing harmful drinking' (NICE public health guidance 24, 2010), Available from http://guidance.nice.org.uk/PH24

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 July 2011.
- Long-acting exenatide for the second-line (dual therapy) or third-line (triple therapy) treatment of type 2 diabetes. NICE technology appraisal. Publication date to be confirmed.
- 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 usually above 11 mmol/litre.

Hypoglycaemia

A blood glucose level below the normal range (usually less than 3 mmol/litre).

Killip class

A measure of severity of congestive 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

Damien Longson (Chair)

Consultant Liaison Psychiatrist, Manchester Mental Health & Social Care Trust

Sunil Angris

GP, Staffordshire

Bernard Clarke

Consultant Cardiologist, Central Manchester University Hospital NHS Foundation Trust

Simon Corbett

Consultant Cardiologist, Wessex Cardiothoracic Centre, Southampton University Hospitals NHS Trust

Phillip Dyer

Consultant Physician, Heart of England NHS Foundation Trust, Birmingham

Ian Lewin

Consultant Physician, North Devon Healthcare NHS Foundation Trust

Lesley Mills

Senior Diabetes Nurse Specialist, Warrington and Halton Hospitals NHS Foundation Trust

David Peachey

Patient member

Steven Williams

Consultant Pharmacist in Medicine & Medication Safety, University Hospital of South Manchester NHS Foundation Trust

Short Clinical Guidelines Technical Team

A Short Clinical Guidelines Technical team was responsible for this guideline throughout its development. It prepared information for the Guideline Development Group, drafted the guideline and responded to consultation comments.

Mark Baker
Clinical Adviser

Nicole Elliott
Associate Director

Mendwas Dzingina
Technical Analyst – Health Economics (from February 2011)

Michael Heath
Programme Manager

Kim Jeong
Technical Analyst – Health Economics (June 2010 to February 2011)

Prashanth Kandaswamy
Technical Adviser – Health Economics (June 2010 to March 2011)

Victoria Kelly
Project Manager

Alfred Sackeyfio
Technical Analyst (June 2010 to January 2011)

Abitha Senthinathan
Technical Analyst

Beth Shaw
Technical Adviser (June 2010 to February 2011)

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.

Mr Peter Robb (Chair)
Consultant ENT Surgeon, Epsom & St Helier University Hospitals and The Royal Surrey County NHS Trusts

Dr Aomesh Bhatt
Director of Regulatory & Medical Affairs (North Europe), Reckitt Benckiser Healthcare (UK)

Dr Greg Rogers
GP, Kent

NICE Centre for Clinical Practice

Sarah Willet
Associate Director

Rachel Ryle
Guideline Commissioning Manager

Emma Banks
Guideline Coordinator

Ruaraidh Hill
Technical Lead

Prashanth Kandaswamy (from March 2011)
Health Economist

Anne-Louise Clayton, Susan Burlace
Editors

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 (Ivabradin) 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		
David Peachey	None declared		
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 known or unknown diabetes?

Why this is important

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

It is recommended a large randomised controlled trial is conducted for people with ACS and hyperglycaemia (11 mmol/litre and over) stratified by NSTEMI and STEMI and by known diabetes and unknown 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.