



## **Hyperglycaemia in acute coronary syndromes:**

### **Evidence Update February 2013**

**A summary of selected new evidence relevant to NICE clinical guideline 130 'Management of hyperglycaemia in acute coronary syndromes' (2011)**



Evidence Update 30

Evidence Updates provide a summary of selected new evidence published since the literature search was last conducted for the accredited guidance they relate to. They reduce the need for individuals, managers and commissioners to search for new evidence. Evidence Updates highlight key points from the new evidence and provide a commentary describing its strengths and weaknesses. They also indicate whether the new evidence may have a potential impact on current guidance. For contextual information, this Evidence Update should be read in conjunction with [Hyperglycaemia in acute coronary syndromes \(NICE clinical guideline 130\)](#).

**Evidence Updates do not replace current accredited guidance and do not provide formal practice recommendations.**

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## Introduction

This Evidence Update identifies new evidence that is relevant to, and may have a potential impact on, the following reference guidance:

<sup>1</sup>  [Hyperglycaemia in acute coronary syndromes](#). NICE clinical guideline 130 (2011).


A search was conducted for new evidence from 01 July 2010 to 18 September 2012. A total of 507 pieces of evidence were initially identified. Following removal of duplicates and a series of automated and manual sifts, 4 items were selected for the Evidence Update (see Appendix A for details of the evidence search and selection process). An [Evidence Update Advisory Group](#), comprising topic experts, reviewed the prioritised evidence and provided a commentary.

Although the process of updating NICE guidance is distinct from the process of an Evidence Update, the relevant NICE guidance development centres have been made aware of the new evidence, which will be considered when guidance is reviewed.

## Feedback

If you have any comments you would like to make on this Evidence Update, please email [contactus@evidence.nhs.uk](mailto:contactus@evidence.nhs.uk)

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<sup>1</sup> NICE-accredited guidance is denoted by the Accreditation Mark 

## Key points

The following table summarises what the Evidence Update Advisory Group (EUAG) decided were the key points for this Evidence Update. It also indicates the EUAG's opinion on whether the new evidence may have a potential impact on the current guidance listed in the introduction. For further details of the evidence behind these key points, please see the full commentaries.

The section headings used in the table below are taken from the guidance.

**Evidence Updates do not replace current accredited guidance and do not provide formal practice recommendations.**

Key point	Potential impact on guidance	
	Yes	No
<p><b>Managing hyperglycaemia in inpatients within 48 hours of acute coronary syndrome (ACS)</b></p> <ul style="list-style-type: none"> <li>Intensive insulin control plus sodium chloride 0.9% may reduce platelet reactivity, but may also be associated with an increased risk of hypoglycaemia.</li> <li>Intensive insulin therapy plus glucose with or without potassium does not appear to reduce mortality and may result in an increased risk of hypoglycaemia.</li> </ul>		<p>✓</p> <p>✓</p>
<p><b>Identifying patients with hyperglycaemia after ACS who are at high risk of developing diabetes</b></p> <ul style="list-style-type: none"> <li>Limited evidence suggests that an oral glucose tolerance test pre-discharge appears to be better than measurements of blood glucose, fasting plasma glucose, or HbA<sub>1c</sub> pre-discharge, to detect previously undiagnosed diabetes.</li> <li>Correlation appears to be poor between oral glucose tolerance tests performed the morning after percutaneous coronary revascularisation and repeated 1 month later.</li> </ul>		<p>✓</p> <p>✓</p>

# 1 Commentary on new evidence

These commentaries analyse the key references identified specifically for the Evidence Update. The commentaries focus on the 'key references' (those identified through the search process and prioritised by the EUAG for inclusion in the Evidence Update), which are identified in bold text. Supporting references provide context or additional information to the commentary. Section headings are taken from the guidance.

## 1.1 Managing hyperglycaemia in inpatients within 48 hours of acute coronary syndrome (ACS)

### **Intensive insulin control plus sodium chloride 0.9%**

[NICE CG130](#) recommends that hyperglycaemia in patients admitted to hospital for acute coronary syndromes should be managed by keeping blood glucose levels below 11.0 mmol/litre while avoiding hypoglycaemia. In the first instance, a dose-adjusted insulin infusion with regular monitoring of blood glucose levels should be considered.

A prospective, randomised controlled trial (RCT) by [Vivas et al. \(2011\)](#) evaluated the effect of intensive insulin control (n=59) compared with conventional insulin therapy on platelet aggregation in patients with ACS and hyperglycaemia. All participants had a diagnosis of ACS within the preceding 24 hours plus known diabetes mellitus and blood glucose at admission greater than 120 mg/dl (6.7 mmol/litre), or unknown diabetes mellitus with glucose level greater than 160 mg/dl (8.9 mmol/litre) or between 120–160 mg/dl at admission and greater than 120 mg/dl 1 hour later. Women of childbearing age and people with blood glucose at admission of 400mg/dl (22.2 mmol/litre) or greater were excluded. Participants were randomised to intensive control (target glucose 80–120 mg/dl [4.4 mmol/litre–6.7 mmol/litre]) or conventional control (target glucose  $\leq$ 180 mg/dl [10 mmol/litre]).

The intensive control group received an insulin plus sodium chloride 0.9% infusion during the initial 24 hours according to a predefined algorithm followed by a daily subcutaneous ultra-slow insulin administration supplemented with rapid-acting insulin for meals. The conventional group received rapid-acting insulin using a sliding scale algorithm plus their usual insulin dosage. All participants, unless contra-indicated, received a loading dose of aspirin and clopidogrel on admission, followed by 100 mg aspirin and 75 mg clopidogrel a day. Use of glycoprotein IIb/IIIa inhibitors and the choice of anticoagulant were left to the treating physician. The primary endpoint was the percentage of maximal platelet aggregation following stimulus with adenosine diphosphate (ADP) 20 micromol/litre assessed 24 hours after commencing treatment and at hospital discharge.

Intensive control resulted in a significant reduction in median glucose levels compared with conventional control at 24 hours (115 mg/dl [6.4mmol/litre] vs (157 mg/dl [8.7mmol/litre],  $p<0.001$ ) and at discharge (103mg/dl [5.7mmol/litre] vs 141 mg/dl [7.8 mmol/litre],  $p<0.001$ ). However, hypoglycaemic episodes of less than 60 mg/dl (3.3 mmol/litre) occurred more frequently with the intensive than the conventional control (37.1% vs 1.7%,  $p<0.001$ ). Severe hypoglycaemia (<40mg/dl [2.2 mmol/litre]) was rare (n=2) and only occurred in the intensive control group ( $p=0.26$ ).

After 24 hours, no significant difference was observed in platelet reactivity between the intensive control group (mean standard deviation [SD] 28.9 $\pm$ 22.6%) and conventional control group (mean SD 31.9 $\pm$ 22.7%). The authors stated the lack of difference would have been caused by extensive use of glycoprotein IIb/IIIa inhibitors leading to platelet inhibition. Platelet reactivity was also significantly reduced at discharge in the intensive control group (mean SD 47.9 $\pm$ 13%) compared with the conventional group (mean SD 59.1 $\pm$ 17%,  $p=0.002$ ).

Limitations of the study stated by the authors were that it was too small to find differences in early events or hypoglycaemic episodes and was not designed to evaluate long-term outcomes. The study was also not designed to show whether the effects of intensive glucose control on platelet reactivity were because of insulin administration, glucose normalisation, or both.

Although the intensive control group showed significant reductions in platelet reactivity the results of this study are unlikely to have an impact on [NICE CG130](#) as none of the outcomes showed an effect on cardiovascular events. There may also be an increased risk of hypoglycaemia from this intensive insulin plus sodium chloride 0.9% regimen. In [NICE CG130](#) hyperglycaemia was defined as 11mmol/litre and above, and a large number of the patients in this study would not be considered hyperglycaemic under NICE guidance. Further research is needed on the optimal management of hyperglycaemia in people with ACS who have diagnosed or previously undiagnosed diabetes as indicated in the research recommendation in [NICE CG130](#).

#### **Key reference**

Vivas D, García-Rubira JC, Bernardo E et al. (2011) [Effects of intensive glucose control on platelet reactivity in patients with acute coronary syndromes. Results of the CHIPS study \("Control de Hiperglucemia y Actividad Plaquetaria en Pacientes con Síndrome Coronario Agudo"\)](#) Heart 97: 803–9

#### **Intensive insulin therapy plus glucose**

[NICE CG130](#) recommends that intensive insulin therapy (an intravenous infusion of insulin and glucose with or without potassium) should not be routinely offered to manage hyperglycaemia (blood glucose above 11.0 mmol/litre) in patients admitted to hospital for an ACS unless clinically indicated.

A meta-regression analysis by [Chatterjee et al. \(2012\)](#) evaluated 3 trials that randomised participants (n=2113) to an intensive blood glucose control strategy compared with a less intensive regimen in myocardial infarction. All trials included adults and were irrespective of diabetic status. Intensive blood glucose control was not defined, but all 3 studies used intensive insulin therapy plus glucose with or without potassium. The primary efficacy outcome was all-cause mortality and the primary safety outcome was rate of hypoglycaemic episodes. The secondary outcomes were effects on heart failure, arrhythmias and re-infarction rates.

Intensive blood glucose control had no significant effect on all-cause mortality (relative risk [RR]=0.94, 95% confidence interval [CI] 0.66 to 1.34, p=0.73). Intensive blood glucose lowering in myocardial infarction was associated with significantly higher episodes of hypoglycaemia (RR=13.40, 95% CI 3.69 to 48.61, p<0.01), with a 12% absolute risk increase and a number needed to harm of 9 (95% CI 6.8 to 9.8). Intensive blood glucose lowering therapy also showed no significant improvement in rates of heart failure, arrhythmias and reinfarction. Meta-regression analysis revealed that mortality with intensive blood glucose therapy was worse with increased length of therapy (p=0.001).

The authors stated that they were limited by not being able to review patient-level data. Also, none of the studies that compared intensive glycaemic control achieved their target glucose levels, although they stated that this may overestimate rather than underestimate the risks of intensive therapy.

The results from this meta-regression analysis suggest that intensive insulin therapy does not improve mortality and may result in an increased risk of hypoglycaemia. The 3 included studies in this meta-regression analysis were also considered by [NICE CG130](#) and the results confirm that evidence remains consistent with the recommendation that intensive insulin therapy should not be used in patients with ACS unless clinically indicated and so are unlikely to have an impact on [NICE CG130](#).

### Key reference

Chatterjee S, Sharma A, Lichstein E et al. (2013) [Intensive glucose control in diabetics with an acute myocardial infarction does not improve mortality and increases risk of hypoglycemia - a meta-regression analysis](#). *Current Vascular Pharmacology* 11: 100-4

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

[NICE CG130](#) recommends that all patients with hyperglycaemia after ACS and without known diabetes should be offered tests for: HbA<sub>1c</sub> levels (glycated haemoglobin, an index of average plasma glucose concentration) before discharge and fasting blood glucose levels no earlier than 4 days after the onset of ACS. It also recommends that oral glucose tolerance tests should not be routinely offered to patients with hyperglycaemia after ACS and without known diabetes if HbA<sub>1c</sub> and fasting blood glucose levels are within the normal range.

A substudy of an RCT (n=109) by [de Mulder et al. \(2012\)](#) identified the occurrence of previously undiagnosed diabetes and compared different methods of diagnosing diabetes mellitus in patients with ACS. This was part of the 'BIOMarker study to identify the Acute risk of a Coronary Syndrome' (BIOMArCS 2).

An oral glucose tolerance test was performed with a load of 75 g glucose before discharge and preferably on day 3 of admission. Undiagnosed diabetes was defined as fasting plasma glucose of 7.0 mmol/litre or greater or a plasma glucose of 11.1 mmol/litre or greater 2 hours after the glucose load (referred to as post-load glucose). A post-load glucose measurement was obtained only when the fasting plasma glucose was less than 7.0 mmol/litre. Impaired glucose metabolism was defined as either impaired fasting glucose (fasting plasma glucose=6.1–6.9 mmol/litre) or impaired glucose tolerance (post-load glucose=7.8–11.0 mmol/litre). Patients not included in either group were considered to have normal glucose metabolism.

Patients with a clinical diagnosis of ACS and plasma glucose levels of 7.8–16 mmol/litre were randomised to intensive blood glucose regulation with intravenous insulin or conventional glucose management. The study mainly included men (81%), white people (98%) and patients with ST elevation (84%). ACS was diagnosed as typical ischaemic chest pain for at least 15 minutes plus either ST elevation greater than 1 mm in 2 consecutive leads or elevated markers of myocardial necrosis [troponin I level >0.45 micrograms/litre] within 24 hours after the onset of chest pain. Exclusion criteria included patients with insulin treated diabetes mellitus, left ventricular ejection fraction less than 30%, or plasma creatinine greater than 220 mmol/litre.

The median admission plasma glucose was 9.2 mmol/litre, the median fasting plasma glucose was 5.9 mmol/litre and the median post-load glucose was 9.1 mmol/litre. Diabetes was newly diagnosed in 38 patients (35%), impaired glucose metabolism was found in 48 patients (44%), and normal glucose metabolism was found in 23 patients (21%). Of the 38 patients newly diagnosed with diabetes, fasting plasma glucose diagnosed 14 patients (sensitivity=37% and specificity=100%) and post-load glucose diagnosed 24 patients. Patients with undiagnosed diabetes had a higher admission HbA<sub>1c</sub> (p<0.001). However, the HbA<sub>1c</sub> diagnostic cut-off ( $\geq 6.5\%$  [48 mmol/mol]) detected only 11 (29%) of the 38 patients with diabetes. The sensitivity to detect undiagnosed diabetes with admission plasma glucose (7.8–16 mmol/litre) by HbA<sub>1c</sub> ( $\geq 6.5\%$ ) was 29% and the specificity was 100%.

In patients with undiagnosed diabetes the admission plasma glucose varied between 8 mmol/litre and 16 mmol/litre. An admission plasma glucose cut-off value with reasonable sensitivity and specificity to detect previously undiagnosed diabetes could not be established. The optimal cut-off value at the crossing of sensitivity and specificity curves was an admission



plasma glucose value of 9.3 mmol/litre; however sensitivity and specificity were only 56%. The area under the receiver operating characteristic curve was 0.61 for admission plasma glucose, 0.75 for fasting plasma glucose and 0.72 for HbA<sub>1c</sub>, when the oral glucose tolerance test result was used as the reference. These values suggest that admission plasma glucose, fasting plasma glucose and HbA<sub>1c</sub> poorly detected a difference between patients with a positive and negative oral glucose tolerance test.

Limitations of the study stated by the authors were that the number of patients in the study was relatively small and that larger confirmatory studies are needed. It was also not possible to assess the level of undiagnosed diabetes in patients with admission plasma glucose less than 7.8 mmol/litre because these patients were not eligible for the current study.

A cohort study by [Jimenez-Navarro et al. \(2010\)](#) assessed patients (n=88) with ACS and no known diabetes mellitus who had undergone successful percutaneous revascularisation because of ischaemic heart disease. Patients received a 75 g oral glucose tolerance test the morning after revascularisation (7.7 days ±6 days following admission) and 1 month later. A capillary test was performed to rule out a high plasma glucose concentration (≥7 mmol/litre) before blood tests at baseline and at 2 hours after the oral glucose tolerance test. The patient was considered to have diabetes mellitus before the oral glucose tolerance test if the capillary test was greater than 7 mmol/litre. Impaired glucose tolerance was defined as capillary glucose between 7.8–11.0 mmol/litre and diabetes mellitus if the test was 11.0 mmol/litre or greater.

Patients were excluded if they had undergone angioplasty within 48 hours of an acute myocardial infarction or were haemodynamically unstable. The majority of patients were men (82%) and most patients were diagnosed with ACS (78.5%), with the remainder having stable angina (20.5%). ACS was defined as symptoms compatible with angina with associated risk criteria (electrocardiographic changes, increase in markers of myocardial damage or symptoms of deterioration).

Twelve patients had altered fasting glucose levels and 3 patients had diabetes mellitus and did not complete the oral glucose tolerance test. After the first tolerance test 66 patients (75%) showed some degree of carbohydrate metabolism disorder (36 patients [41%] were positive for glucose intolerance and 30 patients [34%] were positive for diabetes mellitus). After the second tolerance test 1 month later, only 39 patients continued to show a carbohydrate metabolism disorder, 23 patients (26%) were positive for glucose intolerance and 16 patients (18%) were positive for diabetes mellitus. Only 36 patients had the same results in the 2 tolerance tests (41%). Of these, just 9 (30%) of the 30 patients who had been diagnosed with diabetes mellitus after the first tolerance test had the same diagnosis after the second tolerance test. After the second tolerance test, 23 (26%) of the 88 patients still showed glucose intolerance, and 9 (18.2%) had diabetes mellitus.

Limitations stated by the authors are that this study was carried out in patients who had undergone successful percutaneous revascularisation and so may not be applicable to ACS patients who undergo different clinical procedures. They also stated that there was a high prevalence of carbohydrate metabolism disorders in the geographical area of the study, which could have affected the results.

The results of the study by Jimenez-Navarro et al. (2010) question the reliability of oral glucose tolerance test results by showing limited concordance when they were tested after admission and 1 month later. These results are consistent with [NICE CG130](#) in not routinely recommending oral glucose tolerance tests to patients with hyperglycaemia after ACS and without known diabetes.

The results of the study by de Mulder et al. (2012) suggest that an oral glucose tolerance test is the best way to screen for diabetes because HbA<sub>1c</sub> and fasting plasma glucose would miss

a substantial proportion of patients who should be further screened for diabetes. This is inconsistent with [NICE CG130](#), which states that oral glucose tolerance testing should not be offered routinely if fasting plasma glucose and HbA<sub>1c</sub> are within the normal range. However, the guidance recommends that fasting blood glucose should be taken no earlier than 4 days after the onset of ACS because the [full guideline](#) suggests that blood glucose levels would be distorted as a result of an acute event. In this study it was ideally taken on the third day and at this time the authors were unable to determine a cut-off value that had both reasonable sensitivity and specificity. Threshold levels for HbA<sub>1c</sub> and fasting blood glucose levels are not recommended in the guidance so local threshold levels used in the UK may differ from those reported in this study from the Netherlands. Because of the limitations on timing of the blood glucose tests and threshold levels the results of this small study are unlikely to have an impact on [NICE CG130](#).

#### **Key references**

De Mulder M, Oemrawsingh RH, Stam F et al. (2012) [Comparison of diagnostic criteria to detect undiagnosed diabetes in hyperglycaemic patients with acute coronary syndrome](#). *Heart* 98: 37–41

Jiménez-Navarro MF, Garcia-Pinilla JM, Garrido-Sanchez L et al. [Poor reproducibility of the oral glucose test in the diagnosis of diabetes during percutaneous coronary intervention](#). *International Journal of Cardiology* 142: 245–9

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

No new key evidence was found for this section.

## 2 New evidence uncertainties

No new evidence uncertainties were identified during the Evidence Update process, however any uncertainties that may be identified in future will be added to the NHS Evidence [UK Database of Uncertainties about the Effects of Treatments](#) (DUETs). Other uncertainties can be found in the [NICE research recommendations database](#).

UK DUETs was established to publish uncertainties about the effects of treatments that cannot currently be answered by referring to reliable up-to-date systematic reviews of existing research evidence.

# Appendix A: Methodology

## Scope

The scope of this Evidence Update is taken from the scope of the reference guidance:

- [Hyperglycaemia in acute coronary syndromes](#). NICE clinical guideline 130 (2011).

## Searches

The literature was searched to identify studies and reviews relevant to the scope. Searches were conducted of the following databases, covering the dates 01 July 2010 (the end of the search period of the most recent NICE Clinical Guideline 130) to 18 September 2012:

- CDSR (Cochrane Database of Systematic Reviews)
- CENTRAL (Cochrane Central Register of Controlled Trials)
- CINAHL (Cumulative Index to Nursing and Allied Health Literature)
- DARE (Database of Abstracts of Reviews of Effects)
- EMBASE (Excerpta Medica database)
- HTA (Health Technology Assessment) database
- MEDLINE (Medical Literature Analysis and Retrieval System Online)
- NHS EED (Economic Evaluation Database)

Table 1 provides details of the MEDLINE search strategy used, which was adapted to search the other databases listed above. The search strategy was used in conjunction with validated Scottish Intercollegiate Guidelines Network [search filters for RCTs and systematic reviews](#). One additional paper (Chatterjee et al. 2012) was identified outside of the search process.

Figure 1 provides details of the evidence selection process. The long list of evidence excluded after review by the Chair of the EUAG, and the full search strategies, are available on request from [contactus@evidence.nhs.uk](mailto:contactus@evidence.nhs.uk)

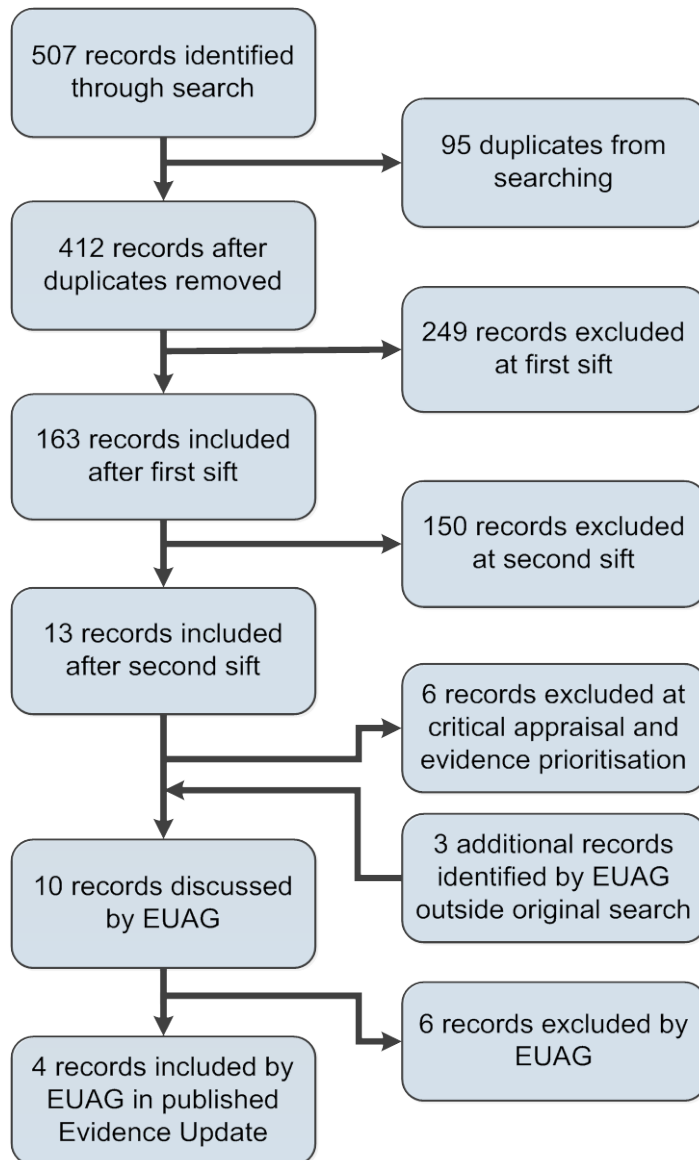
There is more information about [how NICE Evidence Updates are developed](#) on the NHS Evidence website.

**Table 1 MEDLINE search strategy (adapted for individual databases)**

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

24	(myocardial\$ adj3 ischemia\$).tw.	28	(heart\$ adj3 muscle\$ ischemia\$).tw.
25	(myocardial\$ adj3 ischaemia\$).tw.	29	(heart\$ adj3 muscle\$ ischaemia\$).tw.
26	(ischemic\$ adj3 heart\$ disease\$).tw.	30	or/10-29
27	(ischaemic\$ adj3 heart\$ disease\$).tw.	31	9 and 30

**Figure 1 Flow chart of the evidence selection process**



EUAG – Evidence Update Advisory Group



## Appendix B: The Evidence Update Advisory Group and Evidence Update project team

### Evidence Update Advisory Group

The Evidence Update Advisory Group is a group of topic experts who review the prioritised evidence obtained from the literature search and provide the commentary for the Evidence Update.

**Professor Tom Quinn – Chair**

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