Management of stable angina: Evidence Update September 2012

A summary of selected new evidence relevant to NICE clinical guideline 126 'Management of stable angina' (2011)

Evidence Update 23

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 the relevant clinical guideline, available from the NHS Evidence topic page for angina.

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:

[1]**[Management of stable angina](). NICE clinical guideline 126 (2011).**

A search was conducted for new evidence from 22 October 2010 to 10 May 2012. A total of 1142 pieces of evidence were identified and assessed, of which 9 were selected for the Evidence Update (see Appendix A for details of the evidence search and selection process). An Evidence Update Advisory Group, comprised of 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.

Other relevant accredited guidance

The focus of the Evidence Update is on the guidance stated above. However, overlap with other accredited guidance has been outlined as part of the Evidence Update process. Where relevant, this Evidence Update therefore makes reference to the following guidance:

[1][Depression in adults with a chronic physical health problem](). NICE clinical guideline 91 (2009)

Quality standards

[Stable angina](). NICE quality standard 21

Feedback

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

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[1] 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.

Key point	Potential impact on guidance	
	Yes	No
Information and support for people with stable angina • Evidence suggests that identifying depression in people with stable coronary heart disease via a structured assessment is useful.		✓
General principles for treating people with stable angina • There is a lack of robust, clinically meaningful evidence for the use of natriuretic peptides in the prognosis of stable coronary disease.		✓
Anti-anginal drug treatment • Evidence suggests that beta blockers in stable angina do not have a significantly positive or negative effect on mortality versus placebo or other anti-anginal medications.		✓
• Evidence suggests that nitrates in stable angina can improve exercise duration and reduce angina attacks; intermittent administration appeared more effective than continuous administration for exercise duration but the opposite appeared true for angina attacks. The use of nitrates may be limited by side effects.		✓
Investigation and revascularisation • Evidence suggests that both percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) are effective treatments for angina, although PCI appears to have a shorter recovery time, and the rate of repeat revascularisation after CABG appears to be lower.		✓
• Evidence suggests that in patients with stable coronary heart disease who have diabetes, prompt revascularisation (particularly with CABG) appears to be of greater benefit in treating angina (particularly more severe disease) than optimal medical therapy.		✓
• Evidence suggests that in patients with stable coronary heart disease who have diabetes, the relative effect of prompt revascularisation versus optimal medical therapy is unaffected by age. From health status questionnaires, data suggest that in elderly patients the benefits of intervention may be more limited and of a shorter duration than among younger patients.		✓
Pain interventions • Evidence for the use of enhanced external counterpulsation in stable angina is limited and inconclusive.		✓

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   Diagnosis

No new key evidence was found for this section.

1.2   Information and support for people with stable angina

Depression screening

NICE clinical guideline (CG) 126 currently recommends that issues such as concerns about the impact of stress, anxiety or depression on angina should be explored and addressed according to the person's needs.

A prospective cohort study by **Elderon et al. (2011)** investigated the accuracy and prognostic value of depression screening in 1024 patients with stable coronary heart disease. Patients with a history of myocardial infarction (MI), 50% or greater stenosis in 1 or more coronary vessels, exercise-induced ischaemia or a history of coronary revascularisation were selected from 3 medical centres and 9 public health clinics in California, USA. Any patients hospitalised in the previous 6 months for an acute coronary event or who were unable to walk 1 block were excluded.

The study used a 2-step screening method recommended by the American Heart Association (AHA; Lichtman et al. 2008) comprising the 2-item Patient Health Questionnaire (PHQ-2) followed by the 9-item Patient Health Questionnaire (PHQ-9). PHQ-2 consists of 2 'yes or no' questions about feelings over the past month: 'Have you often been bothered by feeling down, depressed or hopeless?' and 'Have you often been bothered by little interest or pleasure in doing things?' PHQ-9 then asks a series of more detailed questions about the nature of the depression over the past 2 weeks requesting a graded response to each question on a scale of 0 to 3. The screening test was performed by self-reported questionnaire, with a positive screen indicated by at least one 'yes' response to PHQ-2 plus a score of 10 or more (maximum score 27) on PHQ-9. As a gold standard comparison, all participants also completed the Computerised Diagnostic Interview Schedule (C-DIS), a structured interview about mood over the past month, the results of which were used to diagnose major depressive disorder (MDD). The C-DIS was performed on the same day as the screening, and the order in which the assessments were performed varied between patients. After the initial assessment, patients were telephoned annually for an average follow-up of 6.3 years to monitor subsequent cardiovascular events (MI, stroke, transient ischaemic attack, heart failure or death).

Based on the 2-step AHA screening method, 187 patients screened positively for depression (of whom 117 had MDD according to C-DIS, and 69 did not have MDD) and 837 screened negatively (of whom 106 had MDD and 730 did not). The MDD status of two participants who did not complete the C-DIS interview was not available. When assessed against the diagnosis of MDD by the C-DIS structured interview, the 2-step AHA screening method had 91% specificity (95% confidence interval [CI] 89 to 93%) but only 52% sensitivity (95% CI 46 to 59%). The positive predictive value (the probability that someone testing positive on screening truly had MDD according to C-DIS) was 63% (95% CI 56 to 70%) and the negative

predictive value was 87% (95% CI 85 to 90%). After adjusting for age, sex, body mass index, history of MI, hypertension, diabetes, heart failure and high-density lipoprotein levels, a positive result from the AHA depression screen was associated with greater risk of subsequent cardiovascular events versus a negative result (adjusted hazard ratio 1.41, 95% CI 1.10 to 1.81, p=0.008). However, when further adjustments were made for behaviours such as smoking, inactivity and non-adherence to medication, the effect was no longer statistically significant (p=0.32), although the authors stated such behaviours may tend to be more prevalent among people with depression.

It should be noted that more than half of the study recruits were from 2 Department of Veterans Affairs medical centres and therefore most participants were men (82%), which may limit generalisability of the evidence.

The results of this study highlight the prevalence of depression among patients with stable coronary heart disease and its potential association with future adverse events, which is consistent with the need to address issues of depression as highlighted in NICE CG126. More detailed advice on depression in this population can be found in 'Depression in adults with a chronic physical health problem' (NICE CG91). This guideline advises being alert to possible depression (particularly in patients with a past history of depression or a chronic physical health problem with associated functional impairment) and to consider asking patients who may have depression the two questions from PHQ-2 (as used in the study), which is consistent with the evidence from the study that identifying depression via a structured assessment is useful.

Key reference
Elderon L, Smolderen KG, Na B et al. (2011) Accuracy and prognostic value of American Heart Association-recommended depression screening in patients with coronary heart disease: data from the Heart and Soul Study. Circulation: Cardiovascular Quality & Outcomes 4: 533–40

Supporting reference
Lichtman JH, Bigger JT, Blumenthal JA et al. (2008) Depression and coronary heart disease: Recommendations for screening, referral, and treatment: A science advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research endorsed by the American Psychiatric Association. Circulation 118: 1768–75

1.3   General principles for treating people with stable angina

Prognostic value of natriuretic peptides

There are currently no recommendations in NICE CG126 regarding the use of biomarkers or any other form of risk stratification to inform the management of stable angina.

In a systematic review and meta-analysis, **Sutaria et al. (2012)** evaluated the relationship between natriuretic peptides and prognosis in prospective studies of people with stable coronary disease followed up for all-cause mortality and coronary or cardiovascular events. For studies to be included, at least 75% of patients needed to have a diagnosis of angina or angiographic disease, or a history of previous acute coronary syndrome at least 2 weeks before natriuretic peptide measurement. Studies were excluded if natriuretic peptides were measured only during admission with an acute coronary syndrome or after a coronary procedure (but before discharge), as were studies in healthy populations and high-risk populations without coronary disease.

A total of 19 studies (n=25,138) were identified, of which 12 were prospective cohorts and 7 used observational data from randomised trials. Length of follow-up varied between 1 and 9.2 years. All of the studies identified for the review were then categorised according to a recent framework published by the AHA (Hlatky et al. 2009). The framework comprised a

proposed set of 6 phases that any new biomarkers should be subject to during the development of an evidence base of their clinical value. Phases 1 and 2 offer initial evidence of prognostic effect; phase 3 demonstrates value beyond existing risk models; phase 4 examines influence on clinical decision making; phase 5 indicates effectiveness in terms of clinical outcomes; and phase 6 assesses cost effectiveness. Of the 19 studies, 17 were categorised as phase 2 (reporting predictive association between natriuretic peptides and future events), and 2 were classed as phase 3 (providing a statistical assessment of whether adding natriuretic peptides to an existing risk model adds further prognostic ability).

A meta-analysis was then performed on 14 of the 17 studies (n=18,841) that were suitable for data pooling. The reported estimates of relative risk (RR) of cardiovascular events associated with natriuretic peptides were taken from each study and converted to a standard scale of effect to allow comparison of the highest third with the lowest third of the natriuretic peptide distribution. Using a random effects model, the comparison resulted in a pooled RR of 3.28 (95% CI 2.45 to 4.38), although the authors reported some heterogeneity between studies. A sub-analysis of the 5 studies (n=5180) that provided adjustment for confounders (age, sex, renal and left ventricular function) reduced the pooled RR to 2.42 (95% CI 1.80 to 3.25).

Limitations of the review included a potential bias introduced by smaller studies reporting higher RRs than larger studies as indicated by a funnel plot. The authors also identified several shortcomings of the included studies as part of their quality assessment (for example, <35% of studies masked assessors to natriuretic peptide measurement, <5% of studies reported sample size calculations or how they handled missing data, no studies prespecified a hypothesis or protocol, and 74% of studies did not report any of the 7 measures recommended by the AHA for evaluating prediction and discrimination of novel risk markers).

The evidence found by the review comprised early-phase studies of limited quality. There is therefore currently a lack of robust, clinically meaningful evidence for the use of natriuretic peptides in prognosis of stable coronary disease. This is consistent with the absence of recommendations from NICE CG126 for the use of biomarkers in prognosis of stable angina.

Key reference

Sutaria S, Philipson P, Fitzpatrick NK et al. (2012) Translational phases of evidence in a prognostic biomarker: a systematic review and meta-analysis of natriuretic peptides and the prognosis of stable coronary disease. Heart 98: 615–22

Supporting reference

Hlatky MA, Greenland P, Arnett DK et al. (2009) Criteria for evaluation of novel markers of cardiovascular risk: a scientific statement from the American Heart Association. Circulation 119: 2408–16

1.4   Anti-anginal drug treatment

Beta blockers

NICE CG126 recommends offering either a beta blocker or calcium channel blocker as first-line treatment for stable angina, with the choice of drug depending on comorbidities, contraindications and the person's preference.

A systematic review and meta-analysis by **Huang and Fox (2012)** investigated the impact of beta blockers on cardiovascular mortality in patients with stable angina. Randomised controlled trials (RCT) of at least 3 weeks involving a comparison of beta blockers with placebo or other anti-anginal drugs were included. Trials including only patients with MI and those that included patients with unstable angina or non-cardiac chest pain, and trials of children, were excluded.

A total of 89 RCTs (n=21,674) were included. After pooling data from all trials, no significant difference in cardiovascular death was found with beta blockers versus any type of control (Peto odds ratio [OR]=0.97, 95% CI 0.86 to 1.09, p=0.59). Further meta-analyses also found no difference in mortality versus placebo only (Peto OR=0.42, 95% CI 0.15 to 1.21, p=0.11; 29 RCTs [mean length of follow-up 13 weeks, median follow-up 8 weeks], n=2315) or versus other anti-anginals (Peto OR=0.98, 95% CI 0.86 to 1.10, p=0.73; 60 RCTs [mean length of follow-up 19 weeks, median follow-up 8 weeks], n=19,343). From sub-analyses, no significant difference in mortality versus placebo was found for cardioselective beta blockers (Peto OR=0.24, 95% CI 0.05 to 1.06, p=0.06; n value not stated) or non-cardioselective beta blockers (Peto OR=0.75, 95% CI 0.17 to 3.32, p=0.70; n value not stated). Results versus other anti-anginals were also non-significant for both cardioselective (p=0.85) and non-cardioselective beta blockers (p=0.09).

For all analyses, the level of heterogeneity between the included trials was deemed small and there was little evidence of any publication bias. The study was potentially limited by the relatively short mean length of follow-up of included trials, particularly for a primary outcome of mortality. A further limitation was the dominance of one large trial of almost 12,500 patients comparing beta blockers with calcium channel blockers (Pepine et al. 2003). The authors also indicated that small unpublished trials were not included in their analysis but stated that this was unlikely to affect results.

Evidence suggests beta blockers do not have a significantly positive or negative impact on mortality versus placebo or other anti-anginals, which is consistent with the recommendation in NICE CG126 to offer them as first-line treatment for stable angina. For cardioselective beta blockers versus placebo, the authors noted that the confidence intervals only just overlapped unity and the p value was close to significance, which may suggest the potential for an impact on mortality. This effect remains unproven and would need to be examined in further research.

Key reference
Huang HL, Fox KA (2012) The impact of beta-blockers on mortality in stable angina: a meta-analysis. Scottish Medical Journal 57: 69–75

Supporting reference
Pepine CJ, Handberg EM, Cooper-DeHoff RM et al. (2003) A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. Journal of the American Medical Association 290: 2805–16

Nitrates

NICE CG126 states that if beta blockers or calcium channel blockers cannot be tolerated, or are contraindicated, or if symptoms are not controlled by one or other of these medications, then second-line treatment with a long-acting nitrate may be considered as monotherapy or as an additional drug.

A systematic review and meta-analysis by **Wei et al. (2011)** studied the effect of nitrates on stable angina. Trials of nitrates (alone or in combination with other anti-anginal drugs) versus placebo, and trials comparing different doses and regimens of nitrates, were included. Comparisons of nitrates with other anti-anginals were excluded. Studies were included only if participants had a diagnosis of stable angina for at least 3 months; studies of patients with acute MI, unstable angina, hepatic failure and renal failure were excluded.

A total of 51 RCTs (n=3595) were included. Pooled analysis evaluating the chronic effect of nitrates (that is, following administration over a number of weeks or months) showed a reduction in the mean number of angina attacks versus placebo of 2.45 episodes per week (95% CI 0.86 to 4.04, p=0.003; 8 RCTs, n=322). Sub-analysis by nitrate regimen showed that

continuous administration (defined as multiple daily oral doses or continuous use of glyceryl trinitrate [GTN] patches) reduced angina attacks by 2.89 episodes per week (95% CI 0.58 to 5.19, p=0.01; 6 RCTs, n=267) whereas intermittent administration (defined as once daily oral sustained release or intermittent use of GTN patches) reduced attacks by 1.5 episodes per week (95% CI 0.92 to 2.08, p<0.00001; 2 RCTS, n=55).

In terms of exercise, a pooled analysis of the chronic effect of nitrates on exercise duration (as measured by exercise tests with a treadmill or bicycle ergometer, performed 1–6 hours after dosage) showed an increase of a mean of 38 seconds versus placebo (95% CI 19 to 58, p=0.0001; 13 RCTs, n=676). In a comparison of nitrate regimens, continuous administration prolonged exercise duration by 31 seconds (95% CI 11 to 51, p=0.002; 10 RCTS, n=406) whereas intermittent administration improved exercise duration by 53 seconds (95% CI 16 to 89, p=0.005; 9 RCTs, n=581).

In terms of adverse effects, headache was reported in most trials and was the main reason for withdrawal. In an analysis of 9 of the included RCTs, 698 of 1352 (51.6%) patients reported headache after receiving nitrates. Quality of life was also assessed in two studies included in the analysis. The first (n=427) found no significant difference between continuous application of GTN patches and placebo, and the second (n=85) found no significant difference between continuous and intermittent application of GTN patches (no numerical data provided for either comparison).

Limitations of the review included the lack of a funnel plot to assess publication bias, and a statement by the authors that none of the studies provided details of randomisation or allocation concealment and so they were unable to make a full quality assessment of the included trials.

The results of this study appear to be broadly consistent with current recommendations in NICE CG126. The data suggest that nitrates can improve exercise duration and angina, but because of potential limitations such as side effects, their role is unlikely to change from second-line treatment following initial therapy with beta blockers and calcium channel blockers.

Key reference
Wei J, Wu T, Yang Q et al. (2011) Nitrates for stable angina: a systematic review and meta-analysis of randomized clinical trials. International Journal of Cardiology 146: 4–12

1.5   Investigation and revascularisation

Percutaneous coronary intervention (PCI) versus coronary artery bypass grafting (CABG)

In people with stable angina whose symptoms are not satisfactorily controlled with optimal medical treatment, NICE CG126 recommends considering revascularisation with either PCI or CABG. No explicit preference is given to either treatment, only that it should be appropriate for the patient. When either procedure would be appropriate and no preference is expressed by the patient, the guideline states that both procedures are effective in relieving symptoms, but there is a potential survival advantage with CABG over PCI for people who have diabetes, or are over 65 years, or have anatomically complex three-vessel disease. The guideline also notes the rate of repeat revascularisation is lower after CABG but that PCI may be more cost effective, and discusses the need to inform patients about practical aspects of CABG and PCI such as the length of hospital stay and recovery time.

In a prospectively designed substudy of the Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) RCT, **Cohen et al. (2011)** examined the effect of PCI with drug-eluting stents versus CABG on health-related quality of life (HRQoL) in 1800 patients with previously untreated three-vessel or left main coronary artery disease (outcomes of death, MI, stroke or

repeat revascularisation from the SYNTAX trial were previously reported by Serruys et al. 2009, which was considered when NICE CG126 was developed). Patients from 85 sites across Europe and the USA were randomised to PCI with paclitaxel-eluting stents (n=903) or CABG (n=897) with the aim of revascularising all vessels of at least 1.5mm in diameter. An assessment of HRQoL was made at baseline and 1, 6 and 12 months using the 100-point Seattle Angina Questionnaire (SAQ; higher scores indicate fewer symptoms and better health status) for disease-specific outcomes, and the Medical Outcomes Study 36-Item Short Form Health-Survey (SF-36) and the European Quality of Life-5 dimensions (EQ-5D) instrument for general health status.

The primary endpoint of score on the SAQ angina-frequency subscale increased by more than 20 points from baseline at 6 and 12 months in both groups (greater than the minimum clinically important difference of 8 to 10 points stated by the authors), but the scores were slightly higher after CABG than PCI at both 6 months (difference of 1.7 points, 95% CI 0.1 to 3.3, p=0.04) and 12 months (difference of 1.7 points, 95% CI 0.2 to 3.2, p=0.03). The proportion of patients free from angina after PCI increased from a mean of 22.2% at baseline to 71.6% at 12 months, and after CABG increased from 22.1% to 76.3% (p=0.05 for difference between groups at 12 months). In terms of general health status, there were no significant differences between groups for the summary measures of SF-36 and EQ-5D at 6 or 12 months, but at 1 month there was a significant benefit with PCI (for example, a difference of 7.7 points in the physical component of SF-36 [p<0.001], which was greater than the minimum clinically important difference of 2.5 to 5 points stated by the authors), indicating a longer recovery period after CABG. The authors pointed out that a value of 7.7 points was greater than the effect on physical health of some chronic conditions such as heart failure (7.2 points).

Limitations of the study included the high proportion of participants who were white (>95%) or male (>75%), and the authors also stated that many patients were excluded from the study on the basis of surgical risk or having an anatomy not favourable to PCI, all of which may affect generalisability of the results. A further limitation was that only approximately 57% of patients had stable angina (although this value was near to the 60% cut-off used as criteria for inclusion in NICE CG126). An issue of missing data was also raised by the authors, although analysis to account for this did not greatly affect results. It should also be noted that the study was funded by the manufacturer of the drug-eluting stents used in all of the PCI procedures.

The evidence suggests that both PCI and CABG are effective treatments for angina, which is consistent with advice in NICE CG126. The minor benefit seen with CABG in this study is unlikely to affect current recommendations. The difference in recovery time between the two treatments is consistent with the need to inform patients of practical aspects of the two procedures as already stated in the guideline.

Boudriot et al. (2011) also investigated PCI with drug-eluting stents versus CABG in a multicentre non-inferiority RCT in Germany of 201 patients with unprotected left main stenosis with or without additional multivessel coronary artery disease. Participants needed to have symptoms of or documented myocardial ischaemia (the exact number with stable angina was not reported, but the rate of previous MI >48 hours before enrolment of below 20% in each arm suggested a population of likely relevance to stable angina). Patients were randomised to PCI with sirolimus-eluting stents (n=100) or CABG (n=101), although 3 patients randomised to PCI subsequently had CABG.

The study objective was to determine whether PCI with sirolimus-eluting stents was not inferior to CABG with regard to the primary endpoint of freedom from major adverse cardiac events, including all-cause death, MI and target vessel revascularisation within 12 months, with a pre-specified maximum allowable difference of 10%. This endpoint was reached in 19.0% of patients after PCI and 13.9% after CABG (difference 5.1%, 95% CI –5.3 to 15.7%,

p=0.19 for non-inferiority). The difference was mainly accounted for by the greater need for repeat revascularisation after PCI compared with CABG (14.0% vs 5.9% respectively, difference 8.1%, 95% CI –0.3 to 17.1%, p=0.35 for non-inferiority). Combined rates of death and MI were similar with both PCI and CABG (5.0% vs 7.9% respectively, p<0.001 for non-inferiority). At a further follow-up of 36.5 months, the results for the combined endpoint and its subcomponents were similar to those at 12 months. The number of patients free from angina was similar after both PCI and CABG (71.1% vs 66.3% respectively, p=0.33).

The authors suggested potential limitations of the study were its sample size, the absence of stroke from the combined endpoint, and that the trial was conducted only in specialist tertiary centres, which may limit the external validity of findings. Each group also included more than 70% men.

The results are similar to those for the unprotected left main subgroup of the SYNTAX trial (previously reported by Serruys et al. 2009) and suggest that PCI and CABG are both effective but repeat revascularisation rate may be lower after CABG, which is consistent with current recommendations in NICE CG126.

Key references
Boudriot E, Thiele H, Walther T et al. (2011) Randomized comparison of percutaneous coronary intervention with sirolimus-eluting stents versus coronary artery bypass grafting in unprotected left main stem stenosis. Journal of the American College of Cardiology 57: 538–45

Cohen DJ, Van Hout B, Serruys PW et al. (2011) Quality of life after PCI with drug-eluting stents or coronary-artery bypass surgery. New England Journal of Medicine 364: 1016–26

Supporting reference
Serruys PW, Morice M-C, Kappetein AP et al. (2009) Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. New England Journal of Medicine 360: 961–72

Revascularisation versus medical therapy in diabetes

NICE CG126 does not make specific recommendations about the choice between revascularisation and medical therapy in people with stable angina who have diabetes. However when choosing between revascularisation procedures where PCI and CABG are both appropriate, it advises taking into account the potential survival advantage of CABG in people who have diabetes, or are over 65 years, or have anatomically complex three-vessel disease.

The Bypass Angioplasty Revascularisation Investigation 2 Diabetes (BARI 2D) RCT compared prompt revascularisation with optimal medical treatment in patients with stable coronary artery disease and type 2 diabetes. Initial analysis of data from this trial by the BARI 2D Study Group (2009) found no significant difference between the interventions on outcomes of all-cause mortality, cardiovascular death, MI and stroke, and this was considered when NICE CG126 was developed. Two recent studies performed additional analyses of evidence from this trial for which commentaries are provided below, following a description of the BARI 2D trial methodology.

BARI 2D recruited people with type 2 diabetes, greater than or equal to 50% stenosis in a major epicardial artery, and myocardial ischaemia identified during a stress test or typical effort angina with epicardial stenosis greater than or equal to 70%. The main exclusion criteria were a clinical indication for immediate revascularisation, coronary revascularisation in the previous 12 months, left main coronary disease, class 3 or 4 heart failure, a glycated haemoglobin level of more than 13%, and a serum creatinine level of more than 177 micromol/litre.

Patients (n=2368) from 49 sites across the USA, Brazil, Canada, Mexico, Austria and the Czech Republic were randomised to a strategy of prompt coronary revascularisation (with

either PCI or CABG) and optimal medical treatment ('REV'), or optimal medical treatment alone with the option of subsequent revascularisation if needed ('MED'). The trial was a 2×2 factorial design with patients initially stratified pre-randomisation to either PCI (806 patients subsequently randomised to MED and 796 to REV) or CABG (385 randomised to MED and 377 to REV), based on a decision made by the responsible physician about the most appropriate intervention for the patient (with the expectation that the most severe disease would be treated with CABG). Once randomised, patients allocated to the REV strategy received revascularisation within 4 weeks, and any patients assigned to the MED strategy who became incapacitated by angina or developed worsening ischaemia despite optimal medical therapy could be recommended for treatment with PCI or CABG (in accordance with the original stratification), which was defined as a 'subsequent revascularisation'. Patients in each study arm were further randomised to either insulin or insulin-sensitising hyperglycaemia treatment. Patients were assessed monthly for 6 months, and then every 3 months for a mean of 5.3 years.

An analysis of the BARI 2D trial data by **Dagenais et al. (2011)** examined main outcomes of worsening, freedom from and new angina, and subsequent coronary revascularisations, in the 2364 participants with satisfactory information on baseline angina status. There was no significant difference in the baseline characteristics of patients between the REV and MED strategies within the PCI and CABG strata. However, compared with patients assigned to PCI, those randomised to CABG were more likely to be older, male, have a higher blood pressure and myocardial jeopardy index, and higher rates of 3-vessel disease (all p<0.001 vs PCI) and previous MI (p=0.004 vs PCI).

For the main outcomes examined by this analysis, at 5-years there was no significant difference between the REV and MED strategies for worsening angina (p=0.438) or freedom from angina (p=0.053), however REV was more effective than MED in terms of lower cumulative rates of new angina (46% vs 59%, p<0.001) and subsequent revascularisations (23% vs 42%, p<0.001). When patients were assessed at 3 years, REV was significantly more effective than MED for all the main outcomes, with lower rates of worsening angina (8% vs 13%, p<0.001), new angina (37% vs 51%, p=0.001) and subsequent revascularisations (18% vs 33%, p=0.001), and a higher rate of angina-free status (66% vs 58%, p=0.003). For worsening angina, the difference between REV and MED was not significant at 2 or 4 years, but for the other main outcomes the significant benefit of REV was sustained over most of the 5 years of follow-up. For worsening angina and freedom from angina, the size of benefit of REV over MED appeared to attenuate over time, particularly after 3 years.

It should be noted that much of the improvement associated with the REV strategy was driven by results with CABG. For example, in the PCI stratum for the outcomes of worsening angina and freedom from angina, a significant advantage of REV over MED was only observed at 1 year whereas in the CABG stratum the significant benefit of REV was sustained for up to 5 years.

Analysis of type of hyperglycaemia treatment showed no effect of insulin versus insulin-sensitising on odds ratios for worsening angina (p=0.7), freedom from angina (p=0.9), or the 5-year cumulative rates of new angina (p=0.3) or subsequent revascularisations (p=0.08).

Potential limitations of the study included the number of participants with angina (although at 61% this was above the 60% cut-off used as criteria for inclusion in NICE CG126), and that only one third of patients who underwent PCI received drug-eluting stents, which the authors considered to be a low rate for this procedure.

The evidence suggests that prompt revascularisation in patients with type 2 diabetes offers greater benefit in treating angina versus optimal medical therapy, particularly for CABG, and particularly during the first few years. In this study, CABG was performed in patients with more severe disease, therefore these data are consistent with current recommendations in

NICE CG126 noting that CABG may be beneficial in a subgroup of patients with diabetes, or who are older, or have more complex disease. The type of hyperglycaemia treatment does not appear to affect angina outcomes in stable coronary artery disease.

Data from the BARI 2D trial were also analysed in a study by **Chung et al. (2011)** to investigate the impact of age on the effectiveness of revascularisation strategies and hyperglycaemia treatments. Patients were categorised into 3 age groups: younger than 60 years (n=939), 60–69 years (n=915), or 70 years and older (n=514). The effect of age on the REV and MED strategies and on type of hyperglycaemia treatment (insulin or insulin-sensitising) were then assessed against clinical outcomes (death from all causes, major cardiovascular events [a composite of death, MI and stroke], cardiac death, and subsequent revascularisation), angina outcomes, and health status outcomes (as measured by 4 instruments: the Duke Activity Status Index [DASI]; the RAND Medical Outcome Study Energy/Fatigue Scale; the RAND Health Distress score; and Self-Rated Health score). For each outcome the interaction of the randomised treatment and age group was calculated.

Over 5 years of follow-up, the relative effect of the REV versus MED strategy was not influenced by age for outcomes of death (p=0.99), major cardiovascular events (p=0.081), cardiac death (p=0.98), subsequent revascularisation (p=0.10 for CABG, p=0.36 for PCI) angina (p=0.98), or health status (p values ranged from 0.064 to 0.87 across the separate instruments). However, a longitudinal mixed model indicated greater relief of angina with REV versus MED over the follow-up period for all age groups (younger than 60 years: OR=0.61, p<0.001; 60–69 years: OR=0.60, p<0.001; 70 years and older: OR=0.71, p=0.032). There was no effect of age on the type of hyperglycaemia treatment for any of the clinical outcomes (p=0.44 for death, p=0.67 for major cardiovascular death, p=0.85 for cardiac death, p=0.72 for subsequent revascularisation) or health status outcomes (p values ranged from 0.13 to 0.31 across the separate instruments).

In terms of health status, older patients seemed to receive a smaller benefit of shorter duration from either REV or MED than younger patients (for example, at 4-year follow-up patients younger than 60 years still exhibited a significant improvement from baseline in DASI and RAND Energy/Fatigue scores [p<0.01], whereas among patients 70 years and older, the DASI score at 4 years was significantly worse than baseline [p<0.01] and the RAND Energy/Fatigue score was not significantly different).

Limitations of the study noted by the authors included not collecting information about arthritis and dementia, which may have been relevant to health status assessment, and missing data for follow-up of health status measures (although multiple imputation and sensitivity analysis to account for this did not substantially change the results).

The data suggest that in people with type 2 diabetes, the relative efficacy of the REV and MED strategies on outcomes of death, major cardiovascular events and revascularisation were unaffected by age, but within each age group REV was more effective than MED for angina relief. The evidence also suggests that in elderly patients, benefits of either approach may be more limited and of a shorter duration than among younger patients. Age does not appear to affect the relative efficacy of hyperglycaemia treatments in stable coronary artery disease. This evidence is unlikely have an impact on NICE CG126.

Key references

Chung S-C, Hlatky MA, Faxon D et al. (2011) The effect of age on clinical outcomes and health status: BARI 2D (Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes). Journal of the American College of Cardiology 58: 810–9

Dagenais GR, Lu J, Faxon DP et al. (2011) Effects of optimal medical treatment with or without coronary revascularization on angina and subsequent revascularizations in patients with type 2 diabetes mellitus and stable ischemic heart disease. Circulation 123: 1492–500

Supporting reference
BARI 2D Study Group (2009) A randomized trial of therapies for type 2 diabetes and coronary artery disease. New England Journal of Medicine 360: 2503–15

1.6   Pain interventions

Enhanced external counterpulsation (EECP)

NICE CG126 states that EECP should not be offered to manage stable angina.

A Cochrane review by **Amin et al. (2010)** investigated the effects of EECP in chronic stable angina or refractory stable angina. One RCT (n=139) was found examining hour-long sessions of EECP once or twice daily for 35 hours over 4 to 7 weeks versus sham treatment. The authors of the Cochrane review deemed the trial to be of poor methodological quality (for example, exclusion of those with severe symptoms of angina), with incomplete reporting of the primary outcome, limited follow-up of secondary outcomes, and flawed statistical analysis. They therefore concluded that the evidence for EECP in stable angina was inconclusive.

The RCT was originally reported on in 1999 and information about it was available during the development of NICE CG126 when the 'do not do' recommendation was made. No subsequently published studies were found by the Cochrane review and thus the results are consistent with the current guideline.

Key reference
Amin F, Al Hajeri A, Civelek B et al. (2010) Enhanced external counterpulsation for chronic angina pectoris. Cochrane Database of Systematic Reviews issue 2: CD007219

1.7   Stable angina that has not responded to treatment

No new key evidence was found for this section.

1.8   Cardiac syndrome X

No new key evidence was found for this section.

2   New evidence uncertainties

During the development of the Evidence Update, the following evidence uncertainties were identified for the NHS Evidence UK Database of Uncertainties about the Effects of Treatments (UK DUETs).

General principles for treating people with stable angina

- Biomarkers in stable coronary artery disease for prognosis

Anti-anginal drug treatment

- Non-cardioselective beta-blockers versus placebo in stable angina for improvement of mortality

- Effectiveness of nitrates compared to percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) for stable angina

Pain interventions

- Enhanced external counterpulsation (EECP) for stable angina (Canadian Cardiovascular Society Grade IV)

Further evidence uncertainties for stable angina can be found in the UK DUETs database and 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:

- Management of stable angina. NICE clinical guideline 126 (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 22 October 2010 (the end of the search period of NICE clinical guideline 126) to 10 May 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)
- PsycINFO

Table 1 provides details of the MEDLINE search strategy used, which was adapted to search the other databases listed above. The original search strategy used in the reference guidance was amended to include a new (as of 2011) MeSH term 'Angina, Stable/'. The search strategy was used in conjunction with validated Scottish Intercollegiate Guidelines Network search filters for RCTs, systematic reviews and diagnostic studies.

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

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	Angina Pectoris/	10	Myocardial Ischemia/
2	Angina, Stable/	11	exp Coronary disease/
3	Microvascular Angina/	12	(coronary adj2 (atherosclerosis or arteriosclerosis)).ti,ab.
4	Angina Pectoris, variant/		
5	((angina$ or cardiac) adj3 (syndrome-x or xs)).ti,ab.	13	(myocardial adj (ischemia or ischaemia)).ti,ab.
6	(angina$ or angor pectoris).ti.	14	(angina$ or stenocardia or stenocardias or chest pain or chest discomfort or angor pectoris).ti,ab.
7	((stable or chronic or refractory or microvascular or exercise induced) adj3 (stenocardia or stenocardias or angina$ or angor pectoris)).ti,ab.		
		15	(10 or 11 or 12 or 13) and 14
8	(stable adj3 coronary).ti,ab.	16	9 or 15
9	or/1-8	17	((unstable or acute coronary or ACS) not stable).ti,ab.
		18	16 not 17

Figure 1 Flow chart of the evidence selection process
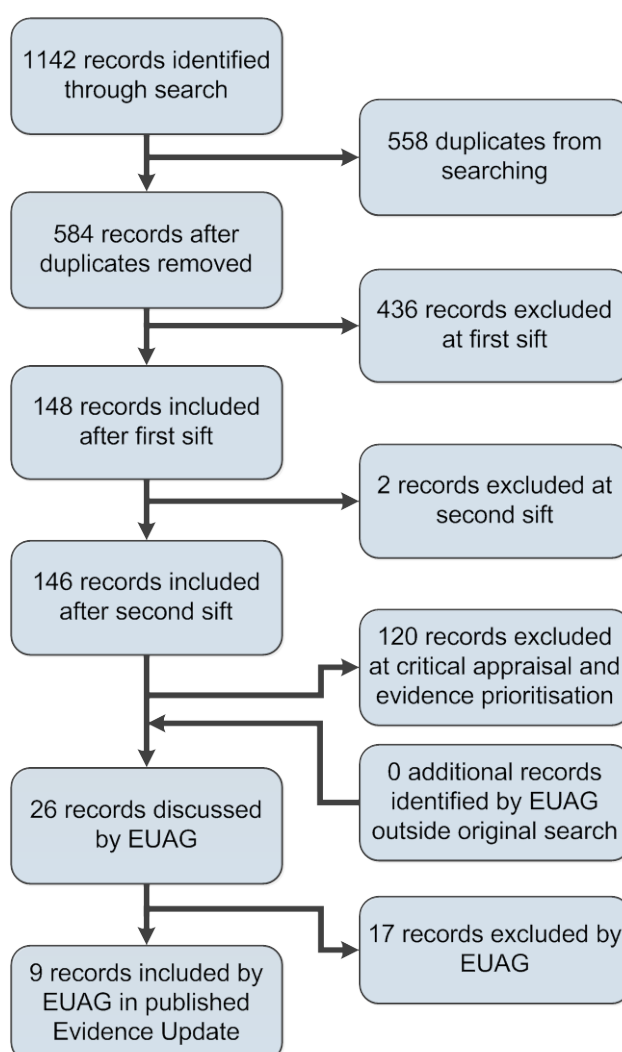
EUAG – Evidence Update Advisory Group

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.

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