

National Institute for Health and Care Excellence

Surveillance programme

Surveillance review consultation document

4-year surveillance review of CG126 Stable angina: management

Background information

Guideline issue date: July 2011
2-year Evidence Update: 2012 (no update)

Surveillance proposal for consultation

We will not update the guideline at this time but will amend the guideline to include a footnote to the recommendations for third-line drug treatments ([1.4.11](#), [1.4.12](#)). This footnote is to make reference to the drug safety updates ([June 2014](#) & [December 2014](#)) regarding the safety concerns with ivabradine.

Reason for the proposal

We found 29 new studies in a search for systematic reviews and randomised controlled trials published between 10 May 2012 and 26 August 2015. We also considered 4 additional studies identified by members of the Guideline Committee who originally worked on this guideline along with 9 studies identified during the 2-year Evidence Update (2012). From all sources, 42 studies were considered to be relevant to the guideline.

This included new evidence on the effectiveness of ivabradine that suggests there is a safety concern regarding an increase in cardiac side-effects. We asked topic experts whether this new evidence would affect current recommendations on ivabradine, or other third-line drugs, and we propose to amend the guideline to refer to this safety concern by adding a footnote to

alert clinicians to the safety alert. Generally, the topic experts thought that an update to the guideline was not needed.

Topic expert feedback highlighted new evidence on diagnostics for stable angina. Intelligence supplied by topic experts may be more relevant to the diagnostic guidelines for chest pain and will be considered at the next surveillance review of that guideline.

We found new intelligence on the use of clopidogrel as an alternative to aspirin for stable angina however a lack of consistent evidence on its effectiveness and limited use in the UK was thought to be insufficient justification to update the guideline.

None of the new evidence on cardiac rehabilitation programmes, anti-anginal drug treatment, revascularisation, prognostic risk stratification, pain interventions or cardiac syndrome X was thought to have an effect on recommendations.

We did not find any new evidence on information and support or general principles for treating people with stable angina.

None of the new evidence considered in surveillance of this guideline was thought to have an effect on current recommendations.

No equalities issues were identified during the process.

See [Appendix 1](#) for further information.

For details of the process and update decisions that are available, see [ensuring that published guidelines are current and accurate](#) in 'Developing NICE guidelines: the manual'

Appendix 1: summary of new evidence

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
Diagnosis			
No questions on diagnosis contained within this guideline as not in scope, however rec 1.1 makes reference to other clinical guidelines for diagnosis. (1.1.1)			
<p>Evidence Update (2012) None identified relevant to this question.</p>	None identified relevant to this question.	<p>Diagnostic tests <i>Comments received via expert feedback:</i> Two topic experts identified a total of five studies regarding diagnostic testing for suspected coronary disease however recognised that diagnosis is beyond the scope of this guideline. One topic expert highlighted an ongoing debate about the role of exercise testing however no further details or supporting evidence provided for this comment.</p>	<p>No new evidence was identified that would affect recommendations. The scope of this guideline does not include diagnosis. However, recommendation 1.1 cross-refers to other clinical guidelines for diagnosis. Intelligence supplied by topic experts may be more relevant to the diagnostic guidelines for chest pain and will be added to the topic issue log. Surveillance decision This review question should not be updated.</p>
Information and support for people with stable angina			
126 – 01 What are the information needs of people with stable angina regarding their condition and its management? (1.2.1–1.2.5 , 1.2.7 , 1.4.2)			
<p>Evidence Update (2012) Depression screening A prospective cohort study¹ investigated the accuracy and prognostic value of depression screening in 1024 patients with stable coronary heart disease. A positive result from the depression screen was associated with greater risk of subsequent cardiovascular events versus a negative result. However, when further</p>	None identified relevant to this question.	None identified relevant to this question.	<p>New evidence is consistent with guideline recommendations. The 2-year Evidence Update found a prospective cohort study¹ investigating the value of depression screening in patients with stable coronary heart disease. The results of this study highlight the prevalence of depression among patients with stable coronary heart disease and its</p>

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
<p>adjustments were made for behaviours such as smoking, inactivity and non-adherence to medication, the effect was no longer statistically significant, although the authors stated such behaviours may tend to be more prevalent among people with depression.</p>			<p>potential association with future adverse events.</p> <p>This is consistent with the current guideline recommendation to explore and address issues of depression in people with stable angina.</p> <p>No new evidence was found by the 4-year surveillance review to change this conclusion or other recommendations within this question.</p> <p>Surveillance decision</p> <p>This review question should not be updated.</p>
<p>126 – 02 What is the clinical/cost effectiveness of cardiac rehabilitation programmes for patients with stable angina? (1.2.6)</p>			
<p>Evidence Update (2012)</p> <p>None identified relevant to this question.</p>	<p>Exercise programme</p> <p>An RCT² to determine the effects of an 8-week exercise training programme (n=32) compared to controls (n=32) on brachial flow-mediated dilation (FMD) in patients with stable coronary artery disease (CAD). After 8 weeks, patients who received exercise training had significant improvements in FMD and exercise capacity compared with controls. However, this study does not report any outcomes relating to angina frequency or improvements.</p> <p>Internet-based programme</p> <p>An RCT³ examined the effectiveness of a 6-week web-based cardiac rehabilitation programme (n=48) compared to GP</p>	<p>Exercise programme</p> <p><i>Comments received via expert feedback:</i></p> <p>One topic expert highlighted the potential role of exercise in management of stable angina and suggests there is inadequate information on this in the guideline.</p>	<p>New evidence is consistent with guideline recommendations.</p> <p>The 4-year evidence review found two RCTs^{2,3} that show potential benefits of exercise programmes on cardiac outcomes. However, only one RCT³ reports any beneficial effect on angina frequency following a cardiac rehabilitation programme.</p> <p>New evidence is consistent with the current guideline recommendation to assess the need for lifestyle advice about exercise and offer interventions as necessary to people with stable angina.</p> <p>Surveillance decision</p> <p>This review question should not be updated.</p>

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	<p>treatment as usual (n=46) for people with angina at 6-week and 6-month follow ups. A significant increase in daily steps walked at the 6-week follow-up was found in the exercise group compared to the control group. Significant intervention effects were observed at the 6-week follow-up in duration of sedentary activity, duration of moderate activity, weight, self-efficacy, emotional quality of life score, and angina frequency. Significant benefits in angina frequency and social quality of life score were also observed at the 6-month follow-up.</p>		
General principles for treating people with stable angina			
126 – 03 What is the clinical /cost effectiveness of short-acting drugs for the management of anginal symptoms? (1.3.3, 1.3.4)			
<p>Evidence Update (2012) None identified relevant to this question.</p>	None identified relevant to this question.	None identified relevant to this question.	<p>No new evidence was identified that would affect recommendations. Surveillance decision This review question should not be updated.</p>
126 – 04 What is the clinical effectiveness of aspirin to improve long term outcomes in people with stable angina? (1.3.5)			
<p>Evidence Update (2012) None identified relevant to this question.</p>	None identified relevant to this question.	None identified relevant to this question.	<p>No new evidence was identified that would affect recommendations. Surveillance decision This review question should not be updated.</p>

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
Clopidogrel			
<p><u>Evidence Update (2012)</u> None identified relevant to this question.</p>	<p>An RCT⁴ of 1001 patients with stable coronary artery disease compared the effect of aspirin to clopidogrel. Primary outcomes consisted of death, myocardial infarction, ischemic stroke and unstable angina. At 2-year follow-up, no overall significant differences in outcomes were found between the interventions. In post-hoc analysis, there were no significant differences in outcomes for patients with aspirin resistance treated with clopidogrel compared to continued aspirin treatment.</p>	<p>Intelligence gathered from NICE Medicines and Prescribing Programme team (MPP) indicates clopidogrel is used in some local NHS services for patients with stable angina. Two local services (Greater Manchester and Barnsley) provided their treatment guidelines for stable angina which includes the use of clopidogrel. However, this use is mostly restricted to people who cannot tolerate aspirin.</p> <p><i>Comments received via Medicines Associates:</i></p> <p>Three Associates identify use of clopidogrel for stable angina patients either at risk of gastrointestinal bleeding or who are unable to take aspirin.</p>	<p>New evidence is unlikely to impact on guideline recommendations.</p> <p>Current recommendation (1.3.5) for secondary prevention of cardiovascular disease considers aspirin for people with stable angina.</p> <p>Clopidogrel as a secondary prevention drug had not been included in the development of the guideline due to being unlicensed at the time. MPP advise that clopidogrel remains unlicensed for stable angina. However, intelligence gathered from Medicines Associates indicates that it may be used in practice as off-license and with people who can't take aspirin.</p> <p>The 4-year evidence review found one RCT⁴ comparing clopidogrel to aspirin. This trial found no benefit of clopidogrel compared to aspirin for stable coronary artery disease or for people with aspirin resistance.</p> <p>Currently, there is a lack of consistent evidence on the effects of clopidogrel in people with stable angina to justify an update of recommendations. Clopidogrel could be an alternative to aspirin if the evidence was sufficient.</p> <p>The next update of CG126 should consider any new evidence on clopidogrel as identified by the 6-year review.</p> <p>Surveillance decision</p>

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
			This recommendation should not be updated.
126 – 05 What is the clinical /cost effectiveness of ACE inhibitors /ARBs for the management of angina? (1.3.6)			
Evidence Update (2012) None identified relevant to this question.	None identified relevant to this question.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. Surveillance decision This review question should not be updated.
126 – 06 What is the clinical/cost effectiveness of angina specific interventions to modify lifestyle/CVD risk factors to reduce symptoms, morbidity and mortality and improve quality of life in angina patients? (1.3.9)			
Evidence Update (2012) None identified relevant to this question.	None identified relevant to this question.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. Surveillance decision This review question should not be updated.
126 – 07 What is the clinical /cost effectiveness of fish oils for reducing symptoms, morbidity, mortality and improving quality of life in stable angina patients? (1.3.9)			
Evidence Update (2012) None identified relevant to this question.	None identified relevant to this question.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. Surveillance decision This review question should not be updated.
126 – 08 What is the clinical /cost effectiveness of Vitamin E for reducing symptoms, morbidity, mortality and improving quality of life in stable angina patients? (1.3.9)			
Evidence Update (2012) None identified relevant to this question.	None identified relevant to this question.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
			Surveillance decision This review question should not be updated.
Anti-anginal drug treatment			
126 – 09 What is the comparative clinical /cost effectiveness of standard antianginal drugs (BBs/CCBs) for the management of angina? (1.4.7, 1.4.8, 1.4.10)			
<p>Evidence Update (2012)</p> <p>Beta blockers</p> <p>A systematic review and meta-analysis⁵ investigated the impact of beta blockers on cardiovascular mortality in patients with stable angina.</p> <p>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 compared to any type of control. Further meta-analyses also found no difference in mortality versus placebo only or versus other antianginals.</p> <p>Although the results suggest beta blockers do not have a significantly positive or negative impact on mortality compared to placebo, this study has two main limitations. Firstly, the mean follow-up time of 19 weeks is relatively short for an outcome of mortality. Secondly, one trial dominated the analysis accounting for almost half the included sample and consisted only of beta blocker to calcium channel blocker comparisons.</p>	<p>Beta blockers</p> <p>A systematic review and meta-analysis⁶ of 26 RCTs (n= 6108) assessed the effects of beta blockers in patients with stable angina. Beta blocker treatment significantly decreased all-cause mortality and incidence of unstable angina when compared with no treatment but had no statistical difference when compared with calcium-channel blocker. Nitrate consumption significantly reduced with beta blockers compared to calcium-channel blockers but not when compared to placebo. Type of intervention made no significant difference to angina frequency.</p>	<p>None identified relevant to this question.</p>	<p>New evidence is unlikely to impact on guideline recommendations.</p> <p>The 2-year Evidence Update found one meta-analysis⁵ comparing beta blockers with placebo or other antianginal drugs. The analysis found no significant difference in cardiovascular death or mortality between beta blockers and comparators. However, this study has two main limitations. Firstly, the mean follow-up time of 19 weeks is relatively short for an outcome of mortality. Secondly, one trial dominated the analysis accounting for almost half the included sample and consisted only of beta blocker to calcium channel blocker comparisons.</p> <p>The 4-year evidence review found one meta-analysis⁶ comparing beta blockers with placebo or calcium channel blocker. The analysis found beta blockers to be no more effective than other antianginal drugs for the management of stable angina. A Centre for Reviews and Dissemination commentary on this study notes the low quality of many studies included and concludes that the results should be treated with caution and may</p>

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
			<p>not be reliable.</p> <p>Although this new evidence is inconsistent with the guideline recommendation, the studies have major limitations. This is unlikely to change the current guideline recommendation 1.4.1 to offer either a beta blocker or a calcium channel blocker as first-line treatment for stable angina with the option to switch between antianginal drugs.</p> <p>Surveillance decision</p> <p>This review question should not be updated.</p>
126 – 10 What is the comparative clinical/cost effectiveness of BB vs. BB+CCB for the management of angina? (1.4.1–1.4.6, 1.4.9, 1.4.10, 1.4.13, 1.4.14)			
<p>Evidence Update (2012)</p> <p>None identified relevant to this question.</p>	None identified relevant to this question.	None identified relevant to this question.	<p>No new evidence was identified that would affect recommendations.</p> <p>Surveillance decision</p> <p>This review question should not be updated.</p>
126 – 11 What is the comparative clinical/cost effectiveness of CCB vs. BB+CCB for the management of angina? (1.4.1–1.4.6, 1.4.9, 1.4.10, 1.4.13, 1.4.14)			
<p>Evidence Update (2012)</p> <p>None identified relevant to this question.</p>	None identified relevant to this question.	None identified relevant to this question.	<p>No new evidence was identified that would affect recommendations.</p> <p>Surveillance decision</p> <p>This review question should not be updated.</p>
126 – 12 What is the comparative clinical / cost effectiveness of adding CCB to basic (or standard) anti-anginal treatment for the management of angina? (1.4.1–1.4.6, 1.4.9, 1.4.10, 1.4.13, 1.4.14)			
<p>Evidence Update (2012)</p>	None identified relevant to this question.	None identified relevant to this question.	No new evidence was identified that

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
None identified relevant to this question.			<p>would affect recommendations.</p> <p>Surveillance decision</p> <p>This review question should not be updated.</p>
<p>126 – 13 What is the clinical and cost effectiveness of adding long-acting nitrates to BB and/or CCBs? (1.4.1–1.4.6, 1.4.11, 1.4.12)</p>			
<p><u>Evidence Update (2012)</u></p> <p>Nitrates</p> <p>A systematic review and meta-analysis⁷ 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.</p> <p>A total of 51 RCTs (n=3595) were included. Pooled analyses evaluating the chronic effect of nitrates (that is, following administration over a number of weeks or months) showed a significant reduction in the mean number of angina attacks versus placebo. The effect of nitrates showed a significant increase in exercise duration compared to placebo.</p> <p>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.</p>	<p>Nitrates</p> <p>An RCT⁸ compared the effectiveness of adding long-acting nitrate pentaerythryl tetranitrate (PETN) to beta blockers in patients with stable angina. Compared to placebo (n= 327), PETN (n= 328) provided no additional benefit to total exercise duration at 12-week follow up. However, PETN is no longer available for use in the UK.</p>	None identified relevant to this question.	<p>New evidence is consistent with guideline recommendations.</p> <p>The 2-year Evidence Update found one meta-analysis⁷ comparing the effect of nitrates (alone or added to antianginal drugs) with placebo. This analysis found a significant reduction in angina attacks with the use of nitrates compared to placebo. However, side effects from nitrates may limit their use.</p> <p>The 4-year evidence review found one RCT⁸ comparing the effectiveness of adding PETN to beta blockers with placebo. This trial found no significant difference between nitrates and placebo in exercise duration for patients with stable angina. However, PETN is no longer available for use in the UK and the results of this trial cannot be extrapolated to other long-acting nitrates.</p> <p>This evidence is consistent with the current guideline recommendation to use nitrates as a third-line treatment following initial therapy with beta blockers and calcium channel blockers.</p> <p>However, this recommendation may need to be updated in the future if there are any</p>

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
			<p>changes to the recommendation for ivabradine.</p> <p>Surveillance decision</p> <p>This review question should not be updated.</p>
<p>126 – 14 What is the clinical /cost effectiveness of ivabradine for the management of stable angina? (1.4.1–1.4.6, 1.4.11, 1.4.12)</p>			
<p>Evidence Update (2012)</p> <p>None identified relevant to this question.</p>	<p>Ivabradine vs placebo on heart rate</p> <p>An RCT⁹ from the ASSOCIATE trial assessed the effects of ivabradine in patients with stable angina receiving beta blockers according to baseline heart rate. Patients were randomised to treatment with ivabradine (5 to 7.5mg bid) or placebo for 4 months, in addition to atenolol 50mg. The effect of treatment on exercise tolerance test parameters was analysed in two groups according to baseline heart rate: > 65 bpm (n=418) versus < 65 bpm (n=436). Ivabradine significantly reduced resting heart rate in both groups. Ivabradine significantly reduced heart rate at all stages of exercise. Significant improvements in exercise capacity (total exercise duration, time to limiting angina, angina onset, and 1-mm ST segment depression, were recorded in both heart rate groups.</p>	<p>Ivabradine vs placebo</p> <p><i>Comments received via expert feedback:</i></p> <p>One topic expert highlighted the need to consider the safety concerns regarding ivabradine following the SIGNIFY trial and questions whether this evidence is sufficient to remove ivabradine from the guideline.</p> <p>One topic expert commented that there is no benefit of ivabradine as indicated by the SIGNIFY trial.</p> <p><i>Studies highlighted via expert feedback:</i></p> <p>The SIGNIFY trial¹⁰ compared ivabradine added to standard background therapy to placebo in 19,102 patients who had both stable coronary artery disease without clinical heart failure and a heart rate of 70 beats per minute or more. The primary end point was a composite of death from cardiovascular causes or nonfatal myocardial infarction.</p> <p>At 3 months, the ivabradine group had a lower heart rate than the placebo group. After a median follow-up of 27.8 months, there was no significant difference</p>	<p>New evidence identified that may change current recommendations.</p> <p>The 4-year evidence review found one RCT⁹ comparing the effectiveness of ivabradine with placebo. This study indicates a reduction in heart rate for ivabradine compared to placebo. The RCT also indicates an improvement in exercise capacity when ivabradine is used in addition to a beta blocker compared to placebo in addition to a beta blocker.</p> <p>New intelligence from the 4-year review found one RCT¹⁰ comparing ivabradine added to first-line treatment with placebo. This RCT found ivabradine reduced heart rate however did not improve cardiovascular outcomes compared to placebo. Ivabradine was associated with an increase in death from cardiovascular causes or nonfatal myocardial infarction in patients with activity-limiting angina. The incidence of bradycardia was higher with ivabradine than with placebo. Topic experts highlighted these potential risks of ivabradine as indicated in this study.</p> <p>New intelligence has identified two drug</p>

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
		<p>between the ivabradine group and the placebo group in the incidence of the primary end point, nor were there significant differences in the incidences of death from cardiovascular causes and nonfatal myocardial infarction. Ivabradine was associated with a significant increase in the incidence of the primary end point among patients with activity-limiting angina but not among those without activity-limiting angina. The incidence of bradycardia was significantly higher with ivabradine than with placebo. The addition of ivabradine to standard therapy did not improve outcomes.</p>	<p>safety updates (June 2014 & December 2014) warning of the cardiac side-effects of ivabradine based on the SIGNIFY trial.</p> <p>Surveillance decision</p> <p>This review question should not be updated. A footnote to the recommendations is to be added with reference to the drug safety updates.</p>
<p>126 – 15 What is the clinical /cost effectiveness of nicorandil for the management of stable angina? (1.4.1–1.4.6, 1.4.11, 1.4.12)</p>			
<p><u>Evidence Update (2012)</u> None identified relevant to this question.</p>	<p>Nicorandil after PCI An RCT¹¹ compared nicorandil (n= 50) to placebo (n= 50) in people with diabetes and stable angina following revascularisation with PCI. At 6-month follow up, the nicorandil group showed significantly higher left ventricle ejection fraction and a trend toward lower incidence of major adverse cardiac events compared to the placebo group.</p>	<p>None identified relevant to this question.</p>	<p>New evidence is unlikely to impact on guideline recommendations.</p> <p>The 4-year evidence review found one RCT¹¹ comparing the effect of nicorandil on people with diabetes and stable angina undergoing revascularisation with PCI. When compared to placebo, nicorandil indicated a trend towards lower major adverse cardiac events. However this is a small study (n=100) where the intervention is in conjunction with revascularisation. This trial may not fully indicate the effects of nicorandil as a third-line treatment for stable angina as it examines the cardio-protective effect during PCI.</p> <p>New evidence is unlikely to change</p>

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
			<p>current guideline recommendation which is to consider nicorandil as third-line treatment for stable angina.</p> <p>However, this recommendation may need to be updated in the future if there are any changes to the recommendation for ivabradine.</p> <p>Surveillance decision</p> <p>This review question should not be updated.</p>
<p>126 – 16 What is the clinical/cost effectiveness of ranolazine for the management of stable angina? (1.4.1–1.4.6, 1.4.11, 1.4.12)</p>			
<p>Evidence Update (2012)</p> <p>None identified relevant to this question.</p>	<p>Ranolazine + BB or CCB</p> <p>A post-hoc analysis¹² of the CARISA trial to assess the benefit of ranolazine in angina patients (n= 258) treated with maximally-tolerated doses of beta blocker or calcium channel blocker. Found a significant change from baseline in total exercise duration after 12 weeks compared to placebo. The number of angina attacks per week compared to baseline was significantly reduced compared to placebo. The effects of ranolazine 750mg and 1000mg were similar and the beneficial effects of ranolazine in this subgroup of maximally-treated patients were consistent with those not on maximally-tolerated doses of the background therapy. The CARISA trial informed the recommendation in CG126 and this analysis supports the placing of ranolazine in the guideline.</p>	<p>Ranolazine as 3rd line drug</p> <p><i>Comments received via expert feedback:</i></p> <p>One topic expert highlighted the need to consider evidence on the potential beneficial effects of ranolazine and suggests it should be moved higher in the list of third-line drugs.</p> <p><i>Studies highlighted via expert feedback:</i></p> <p>An RCT¹³ examined the efficacy of ranolazine versus placebo on weekly angina frequency and sublingual nitroglycerin use in people with type 2 diabetes mellitus, coronary artery disease (CAD) and chronic stable angina who remain symptomatic despite treatment with up to two antianginal agents. After a single-blind, 4-week placebo run-in, patients were randomized to 8 weeks of double-blind ranolazine (target dose 1000mg) or placebo. Angina episodes and nitroglycerin use were recorded with</p>	<p>New evidence is consistent with guideline recommendations.</p> <p>The 4-year evidence review found one post-hoc analysis¹² assessing the effect of ranolazine in patients on maximum doses of first-line treatment for stable angina. Compared to placebo, ranolazine was associated with an improvement in exercise duration and angina attacks.</p> <p>New intelligence from the 4-year review found one RCT¹³ comparing ranolazine to placebo in patients already receiving first-line treatment for stable angina. Compared to placebo, ranolazine was associated with significantly lower frequency of angina attacks.</p> <p>This evidence is consistent with the current guideline recommendation to use ranolazine as a third-line treatment following initial therapy with antianginal treatments for stable angina.</p>

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
		daily entry into a novel electronic diary. Primary outcome was the average weekly number of angina episodes over the last 6 weeks of the study. Weekly angina frequency was significantly lower with ranolazine versus placebo, as was the weekly sublingual nitroglycerin use. There was no difference in the incidence of serious adverse events between groups.	However, this recommendation may need to be updated in the future if there are any changes to the recommendation for ivabradine. Surveillance decision This review question should not be updated.
Investigation and revascularisation			
126 – 17 What is the clinical and cost effectiveness of medical interventions versus CABG in people with stable angina? (1.3.1, 1.3.2, 1.5.1, 1.5.2, 1.5.11–1.5.14)			
Evidence Update (2012) None identified relevant to this question.	None identified relevant to this question.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. Surveillance decision This review question should not be updated.
126 – 18 What is the clinical and cost effectiveness of medical interventions versus PCI in people with stable angina? (1.3.1, 1.3.2, 1.5.1, 1.5.2, 1.5.11–1.5.14)			
Evidence Update (2012) None identified relevant to this question.	Medical vs PCI A meta-analysis ¹⁴ of 12 RCTs comparing PCI to optimal medical therapy (OMT) in patients with stable coronary artery disease (n= 7182). For freedom from angina, there was a significant improved outcome with PCI, as compared with the	Medical vs PCI <i>Comments received via expert feedback:</i> Two topic experts highlighted studies showing the safety and efficacy of revascularisation techniques compared with each other and with medical	New evidence is consistent with guideline recommendations. The 4-year evidence review found two meta-analyses ^{14,15} that compared PCI to optimal medical therapy. Both studies found no significant differences between the interventions for all-cause mortality,

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	<p>OMT group evident at all of the follow-up time points (<1 year, 1-5 years, >5 years). However, PCI was associated with no significant improvement in mortality, cardiac death, nonfatal myocardial infarction, or repeat revascularisation compared with OMT, with consistent results over all follow-up time points.</p> <p>A meta-analysis¹⁵ of 10 RCTs compared PCI and medical therapy for patients with stable angina (n=6752). No differences between PCI and medical therapy found for all-cause mortality, cardiovascular mortality, myocardial infarction, or angina relief at the end of follow-up. These findings support existing guidelines that medical therapy be considered the most appropriate clinical management for patients with stable angina.</p>	<p>treatment.</p> <p>One topic expert commented that the cost of drug-eluting stents has reduced however did not provide any further details or supporting evidence.</p> <p><i>Studies highlighted via expert feedback:</i> A meta-analysis¹⁶ of 5 RCTs compared the effect of PCI and medical therapy (MT) with MT alone exclusively in patients with stable CAD and objectively documented myocardial ischemia on clinical outcomes (n=4064). Found that in patients with stable CAD and objectively documented myocardial ischemia, PCI with MT was not associated with a reduction in death, nonfatal myocardial infarction, unplanned revascularisation, or angina compared with MT alone.</p> <p>PCI guided by fractional flow reserve (FFR)</p> <p><i>Comments received via expert feedback:</i> One topic expert suggests a review of evidence for PCI guided by FFR however recognises that this may not justify a guideline update.</p> <p><i>Studies highlighted via expert feedback:</i> An RCT¹⁷ with 1220 patients with stable coronary artery disease, to assess the fractional flow reserve (FFR) in all stenoses that were visible on angiography. Patients who had at least one stenosis with an FFR of 0.80 or less were randomly assigned to undergo FFR-</p>	<p>cardiac mortality or myocardial infarction. One meta-analysis¹⁴ found a significant improvement from angina following PCI, however, the other meta-analysis¹⁵ found no difference between PCI and optimal medical therapy groups.</p> <p>New intelligence from 4-year surveillance found one meta-analysis¹⁶ comparing PCI with medical therapy. This study found no difference between the interventions in rates of death, myocardial infarction, unplanned revascularisation or angina.</p> <p>Further intelligence identified one RCT¹⁷ comparing fractional flow reserve-guided PCI with medical therapy. This study found FFR-guided PCI reduced the rate of urgent revascularisations, however no differences found in the rates of death or myocardial infarction between the interventions. Medical therapy provided more favourable outcomes for patients without ischemia.</p> <p>NICE is currently developing medical technology guidance on HeartFlow FFRct for the estimation of fractional flow reserve from coronary CT angiography. This technology may impact on recommendations in the future and will be considered at the next review for CG126.</p> <p>New evidence is consistent with the current guideline recommendation to consider medical treatment as first-line in management of stable angina and PCI to be considered if symptoms are not controlled with optimal medical treatment.</p>

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
		<p>guided PCI plus medical therapy or to receive medical therapy alone. Patients in whom all stenoses had an FFR of more than 0.80 received medical therapy alone and were included in a registry. The primary end point was a composite of death from any cause, nonfatal myocardial infarction, or urgent revascularisation within 2 years. Results found the rate of the primary end point was significantly lower in the PCI group than in the medical therapy group. This reduction was driven by a lower rate of urgent revascularisation in the PCI group, with no significant between-group differences in the rates of death and myocardial infarction. Urgent revascularisations that were triggered by myocardial infarction or ischemic changes on electrocardiography were less frequent in the PCI group. The rate of death or myocardial infarction from 8 days to 2 years was lower in the PCI group than in the medical therapy group.</p>	<p>Surveillance decision This review question should not be updated.</p>
<p>126 – 19 What is the clinical and cost effectiveness of medical interventions versus PCI or CABG in people with stable angina? (1.3.1, 1.3.2, 1.5.1, 1.5.2, 1.5.11–1.5.14)</p>			
<p><u>Evidence Update (2012)</u> Revascularisation versus medical therapy in diabetes The Bypass Angioplasty Revascularisation Investigation 2 Diabetes (BARI 2D) RCT was considered when CG126 was developed. Two recent</p>	<p>Medical vs PCI vs CABG A post-hoc analysis²⁰ of the MASS II RCT with a follow up of 10 years evaluated left ventricle ejection fraction (LVEF) in patients with stable coronary artery disease treated by CABG, PCI or medical therapy. Of the 611 patients assessed for LVEF prior to randomisation, 350 were</p>	<p>Medical vs PCI vs CABG <i>Studies highlighted via expert feedback:</i> Meta-analysis²³ of RCTs comparing treatment options for coronary artery disease (CAD) specifically in women. The comparisons were PCI versus coronary artery bypass surgery (CABG) versus</p>	<p>New evidence is consistent with guideline recommendations. The 2-year Evidence Update found two additional analyses^{18,19} of the BARI 2D RCT which compared revascularisation (PCI or CABG) with optimal medical treatment in patients with stable coronary</p>

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
<p>studies performed additional analyses of evidence from this trial.</p> <p>BARI 2D recruited patients with stable coronary artery disease and type 2 diabetes (n=2368) from 49 sites who 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').</p> <p>An analysis¹⁸ of the BARI 2D trial data examined main outcomes of worsening, freedom from angina, new angina and subsequent coronary revascularisations. At 5-year follow up, there was no significant difference between the REV and MED strategies for worsening angina or freedom from angina. However, REV was more effective than MED in terms of lower cumulative rates of new angina and subsequent revascularisations. At 3-year follow up, REV was significantly more effective than MED for all the main outcomes, with lower rates of worsening angina, new angina and subsequent revascularisations, and a higher rate of angina-free status. 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.</p> <p>The evidence suggests that prompt</p>	<p>reassessed at follow up (108 patients from MT, 111 from CABG, and 131 from PCI). There was no significant difference in LVEF at the beginning or at the end of follow-up between the medical treatment and revascularisation groups.</p> <p>A meta-analysis²¹ compared medical treatment to revascularisation (PCI or CABG) among patients with stable coronary artery disease (100 trials with 93,553 patients included). CABG was associated with a survival benefit compared with medical treatment. New generation drug eluting stents (everolimus and zotarolimus) but not balloon angioplasty or other stent types were associated with improved survival compared with medical treatment. CABG reduced the risks of myocardial infarction and subsequent revascularisation compared with medical treatment. New generation drug eluting stents reduced the risk of revascularisation compared with medical treatment.</p> <p>Medical vs PCI vs CABG for patients aged 65 or more</p> <p>An RCT²² from the MASS II trial compared rates of overall mortality, acute myocardial infarction and new revascularisations during 10 year follow up in patients (n= 611) with coronary artery disease. Patients separated</p>	<p>optimal medical therapy in stable or unstable angina. The endpoints assessed were clinical outcomes, modifiers of effectiveness by demographic and clinical factors, and safety outcomes.</p> <p>For women with stable angina randomised to revascularisation (PCI or CABG) or medical therapy, three studies showed a reduction in the composite outcome of death/MI/repeat revascularisation at 5 years for revascularisation with either PCI or CABG. For stable and unstable angina trials comparing PCI with CABG, two studies suggested a benefit of PCI in mortality at 30 days however this was not statistically significant. At 1 year and beyond, although suggestive of a benefit of CABG for the composite outcomes of death/MI/stroke for women, this finding was not statistically significant and represented wide confidence intervals. Found that the few trials reporting sex-specific data on revascularisation compared with optimal medical therapy for stable angina showed a greater benefit with revascularisation for women, while the men in the study fared equally well with either treatment. In contrast, previous meta-analyses that combined results for men and women found similar outcomes for either treatment.</p>	<p>artery disease and type 2 diabetes.</p> <p>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. Age did not affect outcomes of death, major cardiovascular events and revascularisation. However the effects of either medical treatment or revascularisation may be more limited in an older population.</p> <p>The 4-year evidence review found one post-hoc analysis²⁰, one meta-analysis²¹ and one RCT²² comparing medical treatment with revascularisation in patients with stable coronary artery disease.</p> <p>The post-hoc analysis found no difference in left ventricle ejection fraction between patients with stable coronary artery disease treated with CABG, PCI or medical treatment.</p> <p>The meta-analysis found significant benefits of CABG for survival, reduced myocardial infarction and subsequent revascularisation compared to medical treatment. New generation drug-eluting stents were associated with improved survival and reduced revascularisation compared to medical treatment.</p> <p>The RCT compared revascularisation (PCI or CABG) with medical treatment specifically in older patients. The trial found no significant difference in overall survival between the CABG, PCI and</p>

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
<p>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.</p> <p>Data from the BARI 2D trial were also analysed in a study¹⁹ 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.</p> <p>Over 5 years of follow-up, the relative effect of the REV versus MED strategy was not influenced by age for outcomes of death, major cardiovascular events,</p>	<p>according to age with 200 patients aged 65 or more randomised to medical therapy (n= 68), PCI (n= 68) and CABG (n= 64). At 10 years, there was no significant difference in overall survival between the treatment groups. There was a significant reduction of coronary events with CABG compared to PCI or medical treatment. The incidence of revascularisation was significantly lower with CABG compared to PCI or medical treatment. PCI was associated with a higher incidence of myocardial infarction in older patients compared to younger patients.</p>		<p>medical treatment groups. A significant reduction of coronary events and incidents of revascularisation was found for CABG compared to PCI or medical treatment.</p> <p>New intelligence from 4-year surveillance found one meta-analysis²³ comparing revascularisation (PCI or CABG) with medical treatment specifically in women with coronary artery disease. Revascularisation was associated with a reduction in outcomes of death, myocardial infarction or repeat revascularisation compared to medical treatment.</p> <p>The new evidence is consistent with guideline recommendations to consider revascularisation for people with stable angina whose symptoms are not controlled with optimal medical treatment. The evidence is consistent with current recommendations noting that CABG may be beneficial in a subgroup of patients with diabetes, or who are older, or have more complex disease.</p> <p>Surveillance decision</p> <p>This review question should not be updated.</p>

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
<p>cardiac death, subsequent revascularisation, angina, or health status. However, a longitudinal mixed model indicated greater relief of angina with REV versus MED over the follow-up period for all age groups. There was no effect of age on the type of hyperglycaemia treatment for any of the clinical outcomes or health status outcomes. In terms of health status, older patients seemed to receive a smaller benefit of shorter duration from either REV or MED than younger patients.</p> <p>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.</p>			
<p>126 – 20 In adults with stable angina, what is the clinical/cost effectiveness of revascularisation techniques to alleviate angina symptoms and to improve long term outcomes? (1.5.3–1.5.10)</p>			
<p>Evidence Update (2012) PCI vs CABG A prospectively designed substudy²⁴ of the SYNTAX trial examined the effect of</p>	<p>PCI vs CABG A meta-regression²⁶ of RCTs (n= 12,844) to test whether an interaction existed between baseline clinical features (age,</p>	<p>PCI vs CABG <i>Comments received via expert feedback:</i> Two topic experts identified studies that indicate a mortality benefit of</p>	<p>New evidence is consistent with guideline recommendations. The 2-year Evidence Update found one prospectively designed substudy²⁴ of the</p>

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
<p>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 and considered when CG126 was developed.</p> <p>The primary endpoint of score on the 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 and 12 months. The proportion of patients free from angina after PCI or CABG significantly increased at 12 month follow up compared to baseline. In terms of general health status, there were no significant differences between groups at 6 or 12 months, but at 1 month there was a significant benefit with PCI.</p> <p>An RCT²⁵ also investigated PCI with drug-eluting stents versus CABG in 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</p>	<p>gender, diabetes mellitus, previous myocardial infarction and ejection fraction) and choice of revascularisation (PCI or CABG), focusing on death, myocardial infarction, repeat revascularisation and stroke for patients with stable angina. Compared to CABG, PCI significantly reduced the risk of stroke, both at 30 days and at 12-month follow up. This reduction in stroke was significantly higher in females. For repeat revascularisation, PCI performed worse than CABG, both in the overall population and in patients with multivessel disease. Women and those with diabetes mellitus were at significant increased risk of subsequent revascularisation after PCI.</p> <p>An RCT²⁷ compared CABG (n= 935) and PCI using drug-eluting stents (n= 945) on health status in patients with multivessel coronary artery disease and diabetes mellitus. Health status was assessed using the Seattle Angina Questionnaire at baseline, at 1, 6, and 12 months, and annually thereafter. For patients with diabetes and multivessel CAD, CABG surgery provided significantly greater benefit at 2-year follow up on angina frequency, physical limitations and quality of life than PCI using drug-eluting stents. The magnitude of benefit was small, without consistent differences beyond 2 years.</p>	<p>revascularisation with CABG compared to PCI.</p> <p><i>Studies highlighted via expert feedback:</i> A 5-year follow-up²⁸ of the SYNTAX trial, which compared coronary artery bypass graft surgery (CABG) with percutaneous coronary intervention (PCI) for the treatment of patients with left main coronary disease or three-vessel disease, to confirm findings at 1 and 3 years. Patients were randomly assigned to CABG (n=897) or PCI (n=903). CABG should remain the standard of care for patients with complex lesions (high or intermediate SYNTAX scores). For patients with less complex disease (low SYNTAX scores) or left main coronary disease (low or intermediate SYNTAX scores), PCI is an acceptable alternative. All patients with complex multivessel coronary artery disease should be reviewed and discussed by both a cardiac surgeon and interventional cardiologist to reach consensus on optimum treatment.</p> <p>A meta-analysis²⁹ of RCTs to determine the comparative effects of CABG vs PCI on long-term mortality and morbidity found a significant reduction in total mortality with CABG compared with PCI. There were also significant reductions in myocardial infarction and repeat revascularisation with CABG. There was a trend toward excess strokes with CABG, but this was not statistically</p>	<p>SYNTAX trial comparing the effect of PCI to CABG.</p> <p>The evidence suggests that both PCI and CABG are effective treatments for angina, which is consistent with advice in 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.</p> <p>A further RCT²⁵ identified by the 2-year Evidence Update compared PCI with drug-eluting stents versus CABG in patients with unprotected left main stenosis with or without additional multivessel coronary artery disease.</p> <p>The results are similar to those for the unprotected left main subgroup of the SYNTAX trial 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 CG126.</p> <p>The 4-year evidence review found one meta-regression²⁶ and one RCT²⁷ comparing the effects of PCI to CABG in patients with stable angina.</p> <p>The meta-regression found that CABG was associated with significant reductions in repeat revascularisations, especially in sub-groups of women and those with</p>

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
<p>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.</p> <p>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. This endpoint was reached in 19.0% of patients after PCI and 13.9% after CABG. The difference was mainly accounted for by the greater need for repeat revascularisation after PCI compared with CABG. Combined rates of death and MI were similar with both PCI and CABG. 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.</p>		<p>significant. For reduction in total mortality, there was no heterogeneity between trials that were limited to and not limited to patients with diabetes or whether stents were drug eluting or not.</p>	<p>diabetes.</p> <p>The RCT found that CABG provided significantly greater benefit at 2-year follow up on angina frequency, physical limitations and quality of life than PCI in patients with diabetes and multivessel coronary artery disease.</p> <p>This data is consistent with current guideline recommendations to consider CABG over PCI for these sub-groups of patients.</p> <p>New intelligence from 4-year surveillance found one RCT²⁸ analysis comparing CABG to PCI for treatment of left main or three-vessel coronary disease. The analysis found CABG to be superior to PCI for treatment of complex coronary disease, however, PCI found to be an acceptable alternative.</p> <p>A further meta-analysis²⁹ found by 4-year intelligence compared CABG to PCI on long-term outcomes. CABG associated with a significant reduction in mortality, myocardial infarction and repeat revascularisation compared to PCI.</p> <p>These data are consistent with current guideline recommendations to consider either revascularisation (CABG or PCI) options following a discussion with the patient regarding the risks and benefits of each procedure. This should take into account the potential survival benefit of CABG over PCI for people with diabetes, older age or more complex coronary</p>

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
			disease. Surveillance decision This review question should not be updated.
126 – 21 In adults with stable angina what is the incremental value/effectiveness of exercise electrocardiography for prognostic risk stratification in prediction of adverse cardiac outcomes? (1.5.1, 1.5.2, 1.5.11–1.5.14)			
<u>Evidence Update (2012)</u> None identified relevant to this question.	None identified relevant to this question.	<p><i>Comments received via expert feedback:</i> One topic expert identified evidence regarding the role of diagnostic tests for the investigation of chest pain however recognised that diagnosis is beyond the scope of this guideline.</p> <p><i>Studies highlighted via expert feedback:</i> An RCT³⁰ assigned 10,003 symptomatic patients to a strategy of initial anatomical testing with the use of coronary computed tomographic angiography (CTA) or to functional testing (exercise electrocardiography, nuclear stress testing, or stress echocardiography). The composite primary end point was death, myocardial infarction, hospitalisation for unstable angina, or major procedural complication. Secondary end points included invasive cardiac catheterisation that did not show obstructive CAD and radiation exposure. In symptomatic patients with suspected CAD who required non-invasive testing, a strategy of initial CTA, as compared with functional testing, did not improve clinical outcomes over a median follow-up of 2 years.</p>	New evidence is unlikely to impact on guideline recommendations. New intelligence from 4-year surveillance found one RCT ³⁰ comparing anatomical and functional testing to determine differences in clinical outcomes over a 2-year follow up. The study found no improvement in clinical outcomes between the anatomical and functional testing. The impact of this study is limited for this guideline as it relates primarily to diagnosis which is beyond the scope. The population within the study also falls outside the scope of the guideline as it only includes people without a diagnosis, only suspected, coronary artery disease. Surveillance decision This review question should not be updated.

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
126 – 22 In adults with stable angina what is the incremental value/effectiveness of exercise echocardiography for prognostic risk stratification in prediction of adverse cardiac outcomes? (1.5.1, 1.5.2, 1.5.11–1.5.14)			
Evidence Update (2012) None identified relevant to this question.	None identified relevant to this question.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. Surveillance decision This review question should not be updated.
126 – 23 In adults with stable angina what is the incremental value/effectiveness of Myocardial Perfusion Imaging for prognostic risk stratification in prediction of adverse cardiac outcomes? (1.5.1, 1.5.2, 1.5.11–1.5.14)			
Evidence Update (2012) None identified relevant to this question.	None identified relevant to this question.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. Surveillance decision This review question should not be updated.
126 – 24 In adults with stable angina what is the incremental value/effectiveness of “exercise tests and ambulatory ECG” for prognostic risk stratification in prediction of adverse cardiac outcomes? (1.5.1, 1.5.2, 1.5.11–1.5.14)			
Evidence Update (2012) None identified relevant to this question.	None identified relevant to this question.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. Surveillance decision This review question should not be updated.
Pain interventions			
126 – 25 What is the clinical/cost effectiveness of TENS in people with stable angina? (1.6.1)			
Evidence Update (2012) None identified relevant to this question.	None identified relevant to this question.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. Surveillance decision

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
			This review question should not be updated.
126 – 26 What is the clinical/cost effectiveness of EECP in people with stable angina? (1.6.1)			
<p>Evidence Update (2012)</p> <p>Enhanced external counterpulsation (EECP)</p> <p>A Cochrane review³¹ 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 for stable angina was inconclusive.</p> <p>The RCT was originally reported on in 1999 and information about it was available during the development of CG126 when the ‘do not do’ recommendation (1.6.1) was made. No subsequently published studies were found by the Cochrane review and thus the results are consistent with the current guideline.</p>	None identified relevant to this question.	None identified relevant to this question.	<p>New evidence is consistent with guideline recommendations.</p> <p>The 2-year Evidence Update found one Cochrane review³¹ consisting of one RCT investigating the effects of EECP for stable angina. The Cochrane review concluded that the trial was of poor quality with flawed statistical analysis resulting in inconclusive evidence for EECP for stable angina.</p> <p>This is consistent with the current guideline ‘do not do’ recommendation to not offer EECP for people with stable angina.</p> <p>No new evidence was found by the 4-year surveillance review to change this conclusion.</p> <p>Surveillance decision</p> <p>This review question should not be updated.</p>

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
126 – 27 What is the clinical/cost effectiveness of Acupuncture in people with stable angina? (1.6.1)			
<p>Evidence Update (2012) None identified relevant to this question.</p>	<p>Acupuncture vs conventional drugs A meta-analysis³² of 16 RCTs compared acupuncture combined with conventional drugs (ACCD) to conventional drugs alone for angina pectoris. ACCD was superior to conventional drugs alone in reducing the incidence of acute myocardial infarction, relief of angina symptoms and improvement of electrocardiography. Acupuncture alone was superior to conventional drugs for angina symptoms and ECG improvement. ACCD was superior to conventional drugs in shortening the time to onset of angina relief, however, the time to onset was significantly longer for acupuncture alone than for conventional treatment alone. However, the included trials were evaluated as having high or moderate risk of bias and poor quality of evidence.</p> <p>A meta-analysis³³ of 8 RCTs compared acupuncture therapy (n= 372) with conventional drugs (n= 268) in people with stable angina. Acupuncture significantly increased the relief of angina symptoms and improved electrocardiography compared to conventional drugs. No significant difference found in reduction of nitroglycerin between the two groups. The time to onset of angina relief was longer for acupuncture therapy than for</p>	<p>None identified relevant to this question.</p>	<p>Acupuncture vs conventional drugs New evidence is unlikely to impact on guideline recommendations. The 4-year evidence review found two meta-analyses^{32,33} comparing acupuncture with conventional drugs for stable angina. Both studies found acupuncture improved angina symptoms however increased the time to relief from angina. The two meta-analyses highlight serious limitations in the included RCTs with risks of bias, poor quality evidence and limited statistical power. In light of the limitations, the new evidence is unlikely to impact on current guideline 'do not do' recommendation for use of acupuncture for people with stable angina. Surveillance decision This review question should not be updated.</p>

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	traditional medicines. Authors highlight the need for more clinical trials to assess the role of acupuncture for stable angina.		
Spinal cord stimulation therapy			
None identified relevant to this question.	Two relevant studies ^{34,35} identified evaluating the safety and efficacy of spinal cord stimulation for refractory angina. Recommendations in this area are contained in the technology appraisal TA159: Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin (October 2008). This information will be passed onto the TA team for consideration when the topic undergoes the review proposal process.	None identified relevant to this question.	<p>There is no clinical question for this intervention in CG126 however the stable angina pathway notes that spinal cord stimulation is not recommended as a treatment.</p> <p>Recommendations in this area are contained in the technology appraisal TA159: Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin (October 2008). New evidence will be passed onto the NICE Technology Appraisal team for consideration when the topic undergoes the review proposal process.</p> <p>Surveillance decision This recommendation should not be updated.</p>
Stable angina that has not responded to treatment			
126 – 28 What is the clinical/cost effectiveness of self management of pain in people with stable angina? (1.7.1)			
<p>Evidence Update (2012) None identified relevant to this question.</p>	None identified relevant to this question.	None identified relevant to this question.	<p>No new evidence was identified that would affect recommendations.</p> <p>Surveillance decision This review question should not be updated.</p>

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
Cardiac syndrome X			
126 – 29 What is the clinical /cost effectiveness of using standard anti-angina drug therapy (short-acting nitrates, BB, CCB, long-acting nitrates, ACE/ARBs, nicorandil, Ivabradine, Ranolazine,) and /or drugs for secondary prevention in people with syndrome X? (1.8.1–1.8.3)			
<p>Evidence Update (2012) None identified relevant to this question.</p>	<p>Statin + CCB An RCT³⁶ compared effects of combination therapy of statin and CCB with statin alone and CCB alone in patients with cardiac syndrome X (n=68). At 90-day follow up, the coronary flow reserve was significantly improved in the three groups. The time to 1 mm ST segment depression increased significantly in the fluvastatin-treated group, the diltiazem-treated group and the fluvastatin+diltiazem-treated group. Combination treatment with statin and CCB is more effective on endothelial function and exercise tolerance than monotherapy in patients with cardiac syndrome X.</p> <p>Statin treatment for secondary prevention One relevant study³⁷ was identified evaluating the use of statins for stable angina patients requiring PCI. Recommendations for the use of statins have been cross-referred in the guideline from CG181 Cardiovascular disease: risk assessment and reduction, including lipid modification (July 2014).</p>	<p>None identified relevant to this question.</p>	<p>New evidence is unlikely to impact on guideline recommendations. The 4-year evidence review found one RCT³⁶ combining statin and CCB treatment to monotherapy for people with cardiac syndrome X. The study found statin and CCB combination treatment to be more effective than monotherapy in patients with cardiac syndrome X. This is however a small trial (n=68) and does not consider cardiovascular events as end points. Considering the limitations of the new evidence, it is unlikely to change drug treatment recommendations for cardiac syndrome X.</p> <p>Surveillance decision This review question should not be updated.</p>

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
126 – 30 What is the clinical/cost effectiveness and safety of cardiac rehabilitation programmes for people with syndrome X? (No recommendation made in the guideline)			
<p>Evidence Update (2012) None identified relevant to this question.</p>	<p>Cardiac rehabilitation An RCT³⁸ assessed the impact of Phase III cardiac rehabilitation and relaxation on the quality of life (QOL) in patients with cardiac syndrome X. The population consisted of 40 eligible women randomly assigned to progressive muscle relaxation (PMR) (n= 11), phase III cardiac rehabilitation (CR) (n= 11), PMR with phase III CR for 8 weeks at home (n= 11) or control group (n= 7). After phase III CR, relaxation, and combination of CR and relaxation, patients demonstrated significantly improved QOL. The results of post-test multiple comparisons showed that there were statistically significant differences between control and all intervention groups. There was also statistically significant difference between relaxation and combination of phase III CR and relaxation groups.</p>	<p>None identified relevant to this question.</p>	<p>New evidence is unlikely to impact on guideline recommendations. The 4-year evidence review found one RCT³⁸ assessing the effect of a Phase III cardiac rehabilitation programme on the quality of life in patients with cardiac syndrome X. The study found significantly improved quality of life in the rehabilitation group. This trial is limited in the number of included participants for each intervention group (total n=40). There is therefore currently a lack of robust, clinically meaningful evidence for the effectiveness of cardiac rehabilitation programmes for cardiac syndrome X. This is consistent with the absence of recommendations in CG126 for cardiac rehabilitation programmes. Surveillance decision This review question should not be updated.</p>
126 – 31 In adults with Cardiac Syndrome X (i.e. those with chest pain and normal coronary arteries) what is the incremental value/effectiveness of functional tests for prognostic risk stratification in prediction of adverse cardiac outcomes? (No recommendation made in the guideline)			
<p>Evidence Update (2012) None identified relevant to this question.</p>	<p>None identified relevant to this question.</p>	<p>None identified relevant to this question.</p>	<p>No new evidence was identified that would affect recommendations. Surveillance decision This review question should not be</p>

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
			updated.
Risk scores			
126 – 32 In adults with stable angina which tables, equations, engines, models or scoring systems are most reliable/effective for prognostic-risk stratification in prediction of adverse cardiac outcomes? (No recommendation made in the guideline)			
<p>Evidence Update (2012)</p> <p>Prognostic value of biomarkers</p> <p>A meta-analysis³⁹ 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.</p> <p>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.</p> <p>A meta-analysis was performed on 14 of the 19 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, although the authors reported some heterogeneity between studies. A sub-analysis of the 5 studies (n=5180) that provided</p>	<p>Prognostic value of biomarkers</p> <p>An RCT⁴⁰ measured plasma levels of 4 cardiovascular biomarkers, midregional pro-atrial natriuretic peptide (MR-proANP), midregional pro-adrenomedullin (MR-proADM), C-terminal pro-endothelin-1 (CT-proET-1), and copeptin, in 3717 patients with stable coronary artery disease and preserved left ventricular ejection fraction who were randomised to trandolapril or placebo as part of the Prevention of Events With Angiotensin Converting Enzyme (PEACE) trial. Elevated levels of MR-proANP, MR-proADM, and CT-proET-1 were independently associated with the risk of cardiovascular death or heart failure.</p> <p>A meta-analysis⁴¹ of 9 prospective cohort studies assessed the association between N-terminal prohormone B-type natriuretic peptide (NT-proBNP) value and long-term prognosis in patients with stable coronary artery disease. End points included all-cause mortality, cardiovascular mortality and cardiovascular events. In a comparison of individuals in the top quartile with those in</p>	<p>None identified relevant to this question.</p>	<p>New evidence is unlikely to impact on guideline recommendations.</p> <p>The 2-year Evidence Update found one meta-analysis³⁹ that evaluated the relationship between natriuretic peptides and prognosis of people with stable coronary disease. The analysis found a pooled relative risk of 3.28 for cardiovascular events associated with natriuretic peptides.</p> <p>The 4-year evidence review found one RCT and one meta-analysis^{40,41} investigating the prognostic value of biomarkers in patients with stable coronary artery disease.</p> <p>The RCT found elevated levels of MR-proANP, MR-proADM, and CT-proET-1 were independently associated with the risk of cardiovascular death or heart failure.</p> <p>The meta-analysis found that a poor prognosis for mortality or cardiovascular events was significantly increased with the elevation of NT-proBNP.</p> <p>The evidence found by the review comprised early-phase studies of limited quality. The Evidence Update concluded that there was a lack of robust, clinically</p>

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
adjustment for confounders (age, sex, renal and left ventricular function) reduced the pooled RR to 2.42.	the bottom quartile of baseline values of NT-proBNP, the combined adjusted hazard ratio (HR) was 2.74. The combined HRs for the second and third quartiles compared with the first quartile were 1.33 and 1.85, respectively. In a subanalysis grouped by the median value, per 1 standard deviation increase or per 1000 pg/mL increase of NT-proBNP, the overall effect also showed that poor prognosis was significantly increased with the elevation of NT-proBNP.		<p>meaningful evidence for the use of natriuretic peptides in prognosis of stable coronary disease. The new evidence from the 4-year review is unlikely to impact on current guideline recommendations due to these limitations.</p> <p>This is consistent with the absence of recommendations from CG126 for the use of biomarkers in prognosis of stable angina.</p> <p>Surveillance decision This review question should not be updated.</p>
Areas not currently covered in the guideline			
NQ – 01 None identified			
N/A	N/A	N/A	N/A
Research recommendations			
Information and support for people with stable angina			
RR – 01 What is the clinical and cost effectiveness of a self-management plan for people with stable angina?			
<p>Evidence Update (2012) None identified relevant to this question.</p>	None identified relevant to this question.	None identified relevant to this question.	<p>No new evidence was identified that would affect recommendations.</p> <p>Surveillance decision This research recommendation will be considered again at the next surveillance point.</p>

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
RR – 02 Is an 8-week, comprehensive, multidisciplinary, cardiac rehabilitation service more clinically and cost effective for managing stable angina than current clinical practice?			
<p>Evidence Update (2012) None identified relevant to this question.</p>	<p>8-week cardiac rehabilitation An RCT⁴² assigned 42 refractory angina patients to either an 8-week Phase III cardiac rehabilitation program or symptom diary control. Outcomes measured before and after intervention and at 8-week follow-up. Cardiac rehabilitation patients had significantly improved physical ability compared with controls in exercise tests. No differences found between groups for angina frequency or severity. Cardiac rehabilitation participants showed improved Health Anxiety Questionnaire reassurance and York Beliefs anginal threat perception scores.</p>	<p>None identified relevant to this question.</p>	<p>New evidence is unlikely to impact on guideline recommendations. The 4-year evidence review found one RCT⁴² comparing a Phase III cardiac rehabilitation programme with symptom diary control in patients with refractory angina. This trial found cardiac rehabilitation significantly improved physical ability and York Beliefs anginal threat perception compared with controls. However, no difference found in angina frequency and severity between the cardiac rehabilitation and control groups. This trial has limitations with a low participant number (n=42) and short follow up duration of 8 weeks. New evidence to answer the research recommendation is limited and is unlikely to impact on recommendations until further trials are conducted. Surveillance decision This research recommendation will be considered again at the next surveillance point.</p>
Anti-anginal drug treatment			
RR – 03 What is the clinical and cost effectiveness of adding a newer anti-anginal drug (nicorandil, ivabradine or ranolazine) to a calcium channel blocker for treating stable angina?			
<p>Evidence Update (2012) None identified relevant to this question.</p>	<p>Ranolazine + BB or CCB A post-hoc analysis¹² of the CARISA trial to assess the benefit of ranolazine in</p>	<p>Ranolazine as 3rd line drug <i>Studies highlighted via expert feedback:</i> An RCT¹³ examined the efficacy of</p>	<p>New evidence is consistent with guideline recommendations. The 4-year evidence review found one</p>

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
	<p>angina patients (n= 258) treated with maximally-tolerated doses of beta blocker or calcium channel blocker. Found a significant change from baseline in total exercise duration after 12 weeks compared to placebo. The number of angina attacks per week compared to baseline was significantly reduced compared to placebo. The effects of ranolazine 750mg and 1000mg were similar and the beneficial effects of ranolazine in this subgroup of maximally-treated patients were consistent with those not on maximally-tolerated doses of the background therapy. The CARISA trial informed the recommendation in CG126 and this analysis supports the placing of ranolazine in the guideline.</p>	<p>ranolazine versus placebo on weekly angina frequency and sublingual nitroglycerin use in subjects with type 2 diabetes mellitus, coronary artery disease (CAD) and chronic stable angina who remain symptomatic despite treatment with up to two antianginal agents. After a single-blind, 4-week placebo run-in, patients were randomized to 8 weeks of double-blind ranolazine (target dose 1000mg) or placebo. Angina episodes and nitroglycerin use were recorded with daily entry into a novel electronic diary. Primary outcome was the average weekly number of angina episodes over the last 6 weeks of the study. Weekly angina frequency was significantly lower with ranolazine versus placebo, as was the weekly sublingual nitroglycerin use. There was no difference in the incidence of serious adverse events between groups.</p>	<p>post-hoc analysis¹² assessing the effect of ranolazine in patients on maximum doses of first-line treatment, including calcium channel blocker, for stable angina. Compared to placebo, ranolazine was associated with an improvement in exercise duration and angina attacks.</p> <p>New intelligence from the 4-year review found one RCT¹³ comparing ranolazine to placebo in patients already receiving first-line treatment, including calcium channel blocker, for stable angina. Compared to placebo, ranolazine was associated with significantly lower frequency of angina attacks.</p> <p>This evidence is consistent with the current guideline recommendation to use ranolazine as a third-line treatment following initial therapy with antianginal treatments for stable angina.</p> <p>Surveillance decision</p> <p>This research recommendation will be considered again at the next surveillance point.</p>
Investigation and revascularisation			
RR – 04 Do people with stable angina and evidence of reversible ischaemia on non-invasive functional testing who are on optimal drug treatment benefit from routine coronary angiography with a view to revascularisation?			
<p>Evidence Update (2012) None identified relevant to this question.</p>	<p>None identified relevant to this question.</p>	<p>PCI guided by fractional flow reserve (FFR) <i>Comments received via expert feedback:</i> One topic expert suggests a review of evidence for PCI guided by FFR however</p>	<p>New evidence is consistent with guideline recommendations.</p> <p>New intelligence from the 4-year review identified one RCT¹⁷ comparing fractional flow reserve-guided PCI with medical therapy. This study found FFR-guided</p>

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
		<p>recognises that this may not justify a guideline update.</p> <p><i>Studies highlighted via expert feedback:</i></p> <p>An RCT¹⁷ with 1220 patients with stable coronary artery disease, to assess the fractional flow reserve (FFR) in all stenoses that were visible on angiography. Patients who had at least one stenosis with an FFR of 0.80 or less were randomly assigned to undergo FFR-guided PCI plus medical therapy or to receive medical therapy alone. Patients in whom all stenoses had an FFR of more than 0.80 received medical therapy alone and were included in a registry. The primary end point was a composite of death from any cause, nonfatal myocardial infarction, or urgent revascularisation within 2 years. Results found the rate of the primary end point was significantly lower in the PCI group than in the medical therapy group. This reduction was driven by a lower rate of urgent revascularisation in the PCI group, with no significant between-group differences in the rates of death and myocardial infarction. Urgent revascularisations that were triggered by myocardial infarction or ischemic changes on electrocardiography were less frequent in the PCI group. The rate of death or myocardial infarction from 8 days to 2 years was lower in the PCI group than in the medical therapy group.</p>	<p>PCI reduced the rate of urgent revascularisations, however no differences found in the rates of death or myocardial infarction between the interventions. Medical therapy provided more favourable outcomes for patients without ischemia.</p> <p>NICE is currently developing medical technology guidance on HeartFlow FFRct for the estimation of fractional flow reserve from coronary CT angiography. This technology may impact on recommendations in the future and will be considered at the next review for CG126.</p> <p>New evidence is consistent with the current guideline recommendation to consider medical treatment as first-line in management of stable angina and PCI to be considered if symptoms are not controlled with optimal medical treatment.</p> <p>Surveillance decision</p> <p>This research recommendation will be considered again at the next surveillance point.</p>

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
RR – 05 In people with stable angina and multi-vessel disease (including left main stem [LMS] disease) whose symptoms are controlled with optimal drug treatment, would an initial treatment strategy of revascularisation be clinically and cost effective compared with continued drug treatment?			
<p>Evidence Update (2012)</p> <p>PCI vs CABG</p> <p>A prospectively designed substudy²⁴ of the SYNTAX trial 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 and considered when CG126 was developed.</p> <p>The primary endpoint of score on the 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 and 12 months. The proportion of patients free from angina after PCI or CABG significantly increased at 12 month follow up compared to baseline. In terms of general health status, there were no significant differences between groups at 6 or 12 months, but at 1 month there was a significant benefit with PCI.</p> <p>An RCT²⁵ also investigated PCI with drug-eluting stents versus CABG in 201</p>	<p>PCI vs CABG</p> <p>A meta-regression²⁶ of RCTs (n= 12,844) to test whether an interaction existed between baseline clinical features (age, gender, diabetes mellitus, previous myocardial infarction and ejection fraction) and choice of revascularisation (PCI or CABG), focusing on death, myocardial infarction, repeat revascularisation and stroke for patients with stable angina. Compared to CABG, PCI significantly reduced the risk of stroke, both at 30 days and at 12-month follow up. This reduction in stroke was significantly higher in females. For repeat revascularisation, PCI performed worse than CABG, both in the overall population and in patients with multivessel disease. Women and those with diabetes mellitus were at significant increased risk of subsequent revascularisation after PCI.</p> <p>An RCT²⁷ compared CABG (n= 935) and PCI using drug-eluting stents (n= 945) on health status in patients with multivessel coronary artery disease and diabetes mellitus. Health status was assessed using the Seattle Angina Questionnaire at baseline, at 1, 6, and 12 months, and annually thereafter. For patients with diabetes and multivessel CAD, CABG surgery provided significantly greater benefit at 2-year follow up on angina</p>	<p>PCI vs CABG</p> <p><i>Comments received via expert feedback:</i></p> <p>Two topic experts identified studies that indicate a mortality benefit of revascularisation with CABG compared to PCI.</p> <p><i>Studies highlighted via expert feedback:</i></p> <p>A 5-year follow-up²⁸ of the SYNTAX trial, which compared coronary artery bypass graft surgery (CABG) with percutaneous coronary intervention (PCI) for the treatment of patients with left main coronary disease or three-vessel disease, to confirm findings at 1 and 3 years. Patients were randomly assigned to CABG (n=897) or PCI (n=903). CABG should remain the standard of care for patients with complex lesions (high or intermediate SYNTAX scores). For patients with less complex disease (low SYNTAX scores) or left main coronary disease (low or intermediate SYNTAX scores), PCI is an acceptable alternative. All patients with complex multivessel coronary artery disease should be reviewed and discussed by both a cardiac surgeon and interventional cardiologist to reach consensus on optimum treatment.</p>	<p>New evidence is consistent with guideline recommendations.</p> <p>The 2-year Evidence Update found one prospectively designed substudy²⁴ of the SYNTAX trial comparing the effect of PCI to CABG.</p> <p>The evidence suggests that both PCI and CABG are effective treatments for angina, which is consistent with advice in 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.</p> <p>A further RCT²⁵ identified by the 2-year Evidence Update compared PCI with drug-eluting stents versus CABG in patients with unprotected left main stenosis with or without additional multivessel coronary artery disease.</p> <p>The results are similar to those for the unprotected left main subgroup of the SYNTAX trial 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 CG126.</p> <p>The 4-year evidence review found one meta-regression²⁶ and one RCT²⁷</p>

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
<p>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.</p> <p>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. This endpoint was reached in 19.0% of patients after PCI and 13.9% after CABG. The difference was mainly accounted for by the greater need for repeat revascularisation after PCI compared with CABG. Combined rates of death and MI were similar with both PCI and CABG. 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.</p>	<p>frequency, physical limitations and quality of life than PCI using drug-eluting stents. The magnitude of benefit was small, without consistent differences beyond 2 years.</p>		<p>comparing the effects of PCI to CABG in patients with stable angina.</p> <p>The meta-regression found that CABG was associated with significant reductions in repeat revascularisations, especially in sub-groups of women and those with diabetes.</p> <p>The RCT found that CABG provided significantly greater benefit at 2-year follow up on angina frequency, physical limitations and quality of life than PCI in patients with diabetes and multivessel coronary artery disease.</p> <p>This data is consistent with current guideline recommendations to consider CABG over PCI for these sub-groups of patients.</p> <p>New intelligence from 4-year surveillance found one RCT²⁸ analysis comparing CABG to PCI for treatment of left main or three-vessel coronary disease. The analysis found CABG to be superior to PCI for treatment of complex coronary disease, however, PCI found to be an acceptable alternative.</p> <p>These data are consistent with current guideline recommendations to consider either revascularisation (CABG or PCI) options following a discussion with the patient regarding the risks and benefits of each procedure. This should take into account the potential survival benefit of CABG over PCI for people with diabetes, older age or more complex coronary</p>

Summary of evidence from previous surveillance	Summary of new evidence from 4-year surveillance (2015)	Summary of new intelligence from 4-year surveillance (2015)	Impact
			<p>disease.</p> <p>Although it should be noted that the new evidence does not compare revascularisation with continued drug treatment. For this reason, the evidence here may not fully address the research question.</p> <p>Surveillance decision</p> <p>This research recommendation will be considered again at the next surveillance point.</p>

Appendix 2: references

1. 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*. 4:533-540.
2. Luk TH, Dai YL, Siu CW et al. (2012) Effect of exercise training on vascular endothelial function in patients with stable coronary artery disease: a randomized controlled trial. *European Journal of Preventive Cardiology* 19:830-839.
3. Devi R, Powell J, and Singh S. (2014) A web-based program improves physical activity outcomes in a primary care angina population: randomized controlled trial. *Journal of Medical Internet Research* 16:e186.
4. Pettersen AA, Seljeflot I, Abdelnoor M et al. (2012) High On-Aspirin Platelet Reactivity and Clinical Outcome in Patients With Stable Coronary Artery Disease: Results From ASCET (Aspirin Nonresponsiveness and Clopidogrel Endpoint Trial). *Journal of the American Heart Association* 1:e000703.
5. Huang HL and Fox KA. (2012) The impact of beta-blockers on mortality in stable angina: a meta-analysis. *Scottish Medical Journal* 57:69-75.
6. Shu dF, Dong BR, Lin XF et al. (2012) Long-term beta blockers for stable angina: systematic review and meta-analysis. [Review]. *European Journal of Preventive Cardiology* 19:330-341.
7. Wei J, Wu T, Yang Q et al. (7-1-2011) Nitrates for stable angina: a systematic review and meta-analysis of randomized clinical trials. *International Journal of Cardiology* 146:4-12.
8. Munzel T, Meinertz T, Tebbe U et al. (2014) Efficacy of the long-acting nitro vasodilator pentaerithrityl tetranitrate in patients with chronic stable angina pectoris receiving anti-anginal background therapy with beta-blockers: a 12-week, randomized, double-blind, placebo-controlled trial. *European Heart Journal* 35:895-903.
9. Tardif JC, Ponikowski P, Kahan T et al. (30-9-2013) Effects of ivabradine in patients with stable angina receiving beta-blockers according to baseline heart rate: an analysis of the ASSOCIATE study. *International Journal of Cardiology* 168:789-794.
10. Fox K, Ford I, Steg PG et al. (18-9-2014) Ivabradine in stable coronary artery disease without clinical heart failure. *New England Journal of Medicine* 371:1091-1099.
11. Shehata M. (2014) Cardioprotective effects of oral nicorandil use in diabetic patients undergoing elective percutaneous coronary intervention. *Journal of Interventional Cardiology* 27:472-481.
12. Sendon JL, Lee S, Cheng ML et al. (2012) Effects of ranolazine on exercise tolerance and angina frequency in patients with severe chronic angina receiving maximally-tolerated background therapy: analysis from the Combination Assessment of Ranolazine In Stable Angina (CARISA) randomized trial. *European Journal of Preventive Cardiology* 19:952-959.
13. Kosiborod M, Arnold SV, Spertus JA et al. (21-5-2013) Evaluation of ranolazine in patients with type 2 diabetes mellitus and chronic stable angina: results from the TERISA randomized clinical trial (Type 2 Diabetes Evaluation of Ranolazine in Subjects With Chronic Stable Angina). *Journal of the American College of Cardiology* 61:2038-2045.
14. Pursnani S, Korley F, Gopaul R et al. (1-8-2012) Percutaneous coronary intervention versus optimal medical therapy in stable coronary artery disease: a systematic review and meta-analysis of randomized clinical trials. [Review]. *Circulation: Cardiovascular Interventions* 5:476-490.
15. Thomas S, Gokhale R, Boden WE et al. (2013) A meta-analysis of randomized controlled trials comparing percutaneous coronary intervention with medical therapy in stable angina pectoris. [Review]. *Canadian Journal of Cardiology* 29:472-482.

16. Stergiopoulos K, Boden WE, Hartigan P et al. (1-2-2014) Percutaneous coronary intervention outcomes in patients with stable obstructive coronary artery disease and myocardial ischemia: a collaborative meta-analysis of contemporary randomized clinical trials. [Review]. *JAMA Internal Medicine* 174:232-240.
17. De BB, Fearon WF, Pijls NH et al. (25-9-2014) Fractional flow reserve-guided PCI for stable coronary artery disease.[Erratum appears in *N Engl J Med.* 2014 Oct 9;371(15):1465]. *New England Journal of Medicine* 371:1208-1217.
18. Dagenais GR, Lu J, Faxon DP et al. (12-4-2011) 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* 123:1492-1500.
19. Chung SC, Hlatky MA, Faxon D et al. (16-8-2011) 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* 58:810-819.
20. Garzillo CL, Hueb W, Gersh BJ et al. (2013) Long-term analysis of left ventricular ejection fraction in patients with stable multivessel coronary disease undergoing medicine, angioplasty or surgery: 10-year follow-up of the MASS II trial. *European Heart Journal* 34:3370-3377.
21. Windecker S, Stortecky S, Stefanini GG et al. (2014) Revascularisation versus medical treatment in patients with stable coronary artery disease: network meta-analysis.[Erratum appears in *BMJ.* 349:g4605 Note: daCosta, Bruno R [corrected to da Costa, Bruno R]; Siletta, Maria G [corrected to Silletta, Maria G]; Juni, Peter [corrected to Juni, Peter]]. *BMJ* 348:g3859.
22. Rezende PC, Hueb W, Garzillo CL et al. (2013) Ten-year outcomes of patients randomized to surgery, angioplasty, or medical treatment for stable multivessel coronary disease: effect of age in the Medicine, Angioplasty, or Surgery Study II trial. *Journal of Thoracic & Cardiovascular Surgery* 146:1105-1112.
23. Dolor RJ, Patel MR, Melloni C et al. (2013) Treatment strategies for women with coronary artery disease. *Comparative Effectiveness Review* 66
24. Cohen DJ, Van HB, Serruys PW et al. (17-3-2011) Quality of life after PCI with drug-eluting stents or coronary-artery bypass surgery. *New England Journal of Medicine* 364:1016-1026.
25. Boudriot E, Thiele H, Walther T et al. (1-2-2011) Randomized comparison of percutaneous coronary intervention with sirolimus-eluting stents versus coronary artery bypass grafting in unprotected left main stem stenosis.[Erratum appears in *J Am Coll Cardiol.* 2011 Apr 26;57(17):1792]. *Journal of the American College of Cardiology* 57:538-545.
26. D'Ascenzo F, Barbero U, Moretti C et al. (2014) Percutaneous coronary intervention versus coronary artery bypass graft for stable angina: meta-regression of randomized trials. *Contemporary Clinical Trials* 38:51-58.
27. Abdallah MS, Wang K, Magnuson EA et al. (16-10-2013) Quality of life after PCI vs CABG among patients with diabetes and multivessel coronary artery disease: a randomized clinical trial. *JAMA* 310:1581-1590.
28. Mohr FW, Morice MC, Kappetein AP et al. (23-2-2013) Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet* 381:629-638.
29. Sipahi I, Akay MH, Dagdelen S et al. (1-2-2014) Coronary artery bypass grafting vs percutaneous coronary intervention and long-term mortality and morbidity in multivessel disease: meta-analysis of randomized clinical trials of the arterial grafting and stenting era. *JAMA Intern Med* 174:223-230.
30. Douglas PS, Hoffmann U, Patel MR et al. (2-4-2015) Outcomes of anatomical versus functional testing for coronary artery disease. *New England Journal of Medicine* 372:1291-1300.

31. Amin F, Al HA, Civelek B et al. (2010) Enhanced external counterpulsation for chronic angina pectoris. *Cochrane Database of Systematic Reviews* CD007219.
32. Chen J, Ren Y, Tang Y et al. (2012) Acupuncture therapy for angina pectoris: a systematic review. [Review]. *Journal of Traditional Chinese Medicine* 32:494-501.
33. Zhang Z, Chen M, Zhang L et al. (2015) Meta-analysis of acupuncture therapy for the treatment of stable angina pectoris. *International journal of clinical and experimental medicine* 8:5112-5120.
34. Zipes DP, Svorkdal N, Berman D et al. (2012) Spinal cord stimulation therapy for patients with refractory angina who are not candidates for revascularization. *Neuromodulation* 15:550-558.
35. Tsigaridas N, Naka K, Tsapogas P et al. (2015) Spinal cord stimulation in refractory angina. A systematic review of randomized controlled trials. [Review]. *Acta Cardiologica* 70:233-243.
36. Zhang X, Li Q, Zhao J et al. (2014) Effects of combination of statin and calcium channel blocker in patients with cardiac syndrome X. *Coronary Artery Disease* 25:40-44.
37. Lee SW, Hau WK, Kong SL et al. (2012) Virtual histology findings and effects of varying doses of atorvastatin on coronary plaque volume and composition in statin-naive patients: the VENUS study. *Circulation Journal* 76:2662-2672.
38. Feizi A, Ghaderi C, Dehghani MR et al. (2012) Effect of phase III cardiac rehabilitation and relaxation on the quality of life in patients with cardiac syndrome X. *Iranian Journal of Nursing and Midwifery Research* 17:547-552.
39. 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* 98:615-622.
40. Sabatine MS, Morrow DA, Lemos JA et al. (2012) Evaluation of multiple biomarkers of cardiovascular stress for risk prediction and guiding medical therapy in patients with stable coronary disease. *SO: Circulation* 125:233-240.
41. Wei G, Yaqi R, Ningfu W et al. (2013) N-terminal prohormone B-type natriuretic peptide and cardiovascular risk in stable coronary artery disease: a meta-analysis of nine prospective studies. [Review]. *Reviews in Cardiovascular Medicine* 14:e92-e98.
42. Asbury EA, Webb CM, Probert H et al. (2012) Cardiac rehabilitation to improve physical functioning in refractory angina: a pilot study. *Cardiology* 122:170-177.