National Institute for Health and Clinical Excellence

Stable Angina
Consultation Comments Table
15 December 2010 – 9 February 2011

Type	Stakeholder	Order no.	Doc	Page No	Line No	Comments	Developer's response
SH	A. Menarini Pharma UK SRL	1	Full	115	1	To ensure consistency with the algorithm on Page 50, we would suggest adding 'or' after 'a long acting nitrate' and 'ivabradine'.	Thank you for your comment. We have made this change.
SH	A. Menarini Pharma UK SRL	2	Full	127	1	To ensure consistency with the algorithm on Page 50, we would suggest adding 'or' after 'a long acting nitrate' and 'ivabradine'.	Thank you for your comment. We have made this change.
SH	A. Menarini Pharma UK SRL	3	Full	142-144	1	To ensure consistency with the algorithm on Page 50, we would suggest adding 'or' after 'a long acting nitrate' and 'ivabradine'.	Thank you for your comment. We have made this change.
SH	A. Menarini Pharma UK SRL	4	Full	152	1	To ensure consistency with the algorithm on Page 50, we would suggest adding 'or' after 'a long acting nitrate' and 'ivabradine'.	Thank you for your comment. We have made this change
SH	A. Menarini Pharma UK SRL	5	Full	50	1	There is one section in the pharmacotherapy part of the algorithm that we believe warrants adjustment: If both beta-blockers and calcium channel blockers are not tolerated or are contraindicated, monotherapy with a second line therapy is suggested. However, as it stands the algorithm does not then progress from this step. In keeping with the principles of the rest of the guideline, we would suggest that if control is inadequate, an additional second-line therapy should be added, prior to progression to intervention.	Thank you for your comment. There is currently no evidence to support the use of newer anti-anginal agents in combination and the GDG considered that people who remain symptomatic should be considered for revascularisation at this stage.
SH	A. Menarini	6	Full	145	2-9	We are generally in agreement with the	Thank you for your comment. This

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	Pharma UK SRL					summary of evidence, although we feel that the introduction to the product has two omissions. Specifically: 1. The effect of ranolazine on the QT interval is noted but we would like to point out that in the clinical trials programme this did not translate into an increase in risk of arrhythmia. In MERLIN, a study that recruited 6,560 patients recovering from acute coronary syndrome, who would therefore be expected to be particularly at risk of arrhythmia, there was no difference in the risk of symptomatic arrhythmia vs placebo (3.0% vs 3.1%). When patients were assessed using Holter monitoring, ranolazine treatment was associated with significantly fewer arrhythmic episodes. 2. The distinctive attribute of ranolazine is that it does not have a clinically significant effect on either blood pressure or heart rate. This distinguishes it from all other anti-anginal agents and allows it to be used in patients with low baseline blood pressure and/or bradycardia. This aspect of ranolazine's action is of key importance in selecting those patients in whom it is most appropriately used and we believe it should be highlighted in this section.	information is included in the SPC for ranolazine and we have therefore added this information to the introduction.
SH	A. Menarini Pharma UK SRL	7	Full	155	2-15	The GDG states that the clinical and cost effectiveness of adding a newer anti-anginal drug (nicorandil, ivabradine or ranolazine) to	Thank you for your comment. This is a research recommendation. The available evidence is from trials of 6 and 12 weeks

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						a calcium channel blocker for treating stable angina is not known. We would like to point out that, in the ranolazine clinical development programme, 469/823 (57%) of patients in the CARISA study, and all 565 patients in the ERICA study were treated with background calcium channel blocker therapy. Additionally, 1977/6560 (30%) of patients in MERLIN – a study in acute coronary syndrome – were also treated with calcium channel blocker. We therefore believe that there is already a clear understanding of the performance of ranolazine in the context of calcium channel blocker use.	follow up. Longer term clinical and cost effectiveness information is required. We have clarified this in the research recommendation.
SH	AGWS Cardiac and Stroke Network	1	Full	57	21	There was concern from the CRG regarding the recommendation that patients over the age of 65 were considered for CABG over PCI. The CRG were unclear where the evidence for this originated.	Thank you for your comment. This evidence came from the meta-analysis by Hlatky et al which found an interaction between outcomes and younger age.
SH	AGWS Cardiac and Stroke Network	2	Full	58	1	It was felt that this statement was incorrect. The risk of stroke during PCI is less than that for CABG.	Thank you for your comment. This is based on the long term data. There was a significant difference between PCI and CABG for stroke at early follow-up but no significant difference at longer term follow-up. The GDG considered that the diagnosis, severity and clinical implications of stroke after revascularisation procedures are poorly defined in the randomised trials. The clinical experience of the GDG was that

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							symptoms of stroke often resolve after revascularisation procedures and most do not result in long term disability.
SH	AGWS Cardiac and Stroke Network	3	Full	General		There was a concern that revascularisation for asymptomatic patients with severe CAD is not indicated, and the CRG felt that certain patterns of disease should be considered for revascularisation, even if asymptomatic especially if there was evidence of reversible ischaemia.	Thank you for your comment. The remit of the guideline is people with stable angina and not people with asymptomatic coronary artery disease. Following stakeholder comment we have altered the recommendations in this guideline for patient with a diagnosis of Stable Angina who become asymptomatic on medical treatment.
SH	AGWS Cardiac and Stroke Network	4	Full	53	31	The CRG did not agree with this concept as patients with severe coronary artery disease (CAD), particularly left main stem disease may have minimal symptoms and may benefit from revascularisation. It was felt that patients should be considered for coronary angiography to delineate their anatomy. If there is doubt in the diagnosis and the probability of CAD is above 60% then angiography is already recommended in NICE CG 95. There was concern that this guidance may lead to the very late diagnosis if severe CAD.	Thank you for your comment. People in this guideline will already have been diagnosed with Stable Angina according to NICE CG95. Following stakeholder consultation the GDG have changed the recommendations to allow consideration of testing of patients whose symptoms have not resolved with medical treatment who have not had recent functional or anatomical tests.
SH	AGWS Cardiac and Stroke Network	5	Full	57	5	There was a debate as to whether all cases required discussion with both a surgeon and cardiologists. It was accepted that a full MDT is important, but there are many cases with single vessel disease who are suitable for PCI and do not need consideration for	Thank you for your comment. We have altered the recommendation on MDT following stakeholder comments. The recommendation now suggests that cases discussed at MDT should include but not be limited to most patients with LMS

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						CABG.	disease and 3 vessel disease.
SH	British Association for Cardiovascular Prevention and Rehabilitation	1	Full	general		We at the British Association for Cardiovascular Prevention and Rehabilitation (BACPR, formally BACR) welcome that NICE recommend the addressing of self-management skills, psychosocial issues and advice about physical exertion, and applaud that this recommendation is given primacy. However, we also note that the GDG is promoting an outdated view of cardiac rehabilitation (CR) which is not consistent with the BACR standards [1] or with the Department of Health Commissioning Pack for cardiac rehabilitation [2].	Thank you for your comment. We have incorporated the components of the cardiac rehab programmes stated by the Department of Health and British Association for Cardiovascular Prevention and Rehabilitation in the introduction
SH	British Association for Cardiovascular Prevention and Rehabilitation	2	Full	328		refers to the four phases of CR; this is an outdated viewpoint. Cardiac rehabilitation is a supervised programme of 5 components covering lifestyle issues, risk factor management, cardio-protective drug therapy and implantable devices, psychosocial status and quality of life, and long term management. All of these components are underpinned and linked by a common core element of education and support for health behaviour change [1]. Please see the BACR Standards document [1] for a more detailed breakdown of what is included in each of the components. The Department of Health Commissioning Pack for Cardiac Rehabilitation [2] outlines	Thank you for your comment and this information. We have altered the introduction of the chapter.

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						a distinctive patient-care pathway of six stages (replacing the four phases) where a key element before a programme starts is a full medical, risk factor, psychosocial and lifestyle assessment that should immediately follow a diagnosis or step-change in the condition or symptoms, with re-assessments relative to patient goals and needs along this pathway. We ask that references to the phases of CR should be removed.	
SH	British Association for Cardiovascular Prevention and Rehabilitation	3	Full	363		"The GDG preferred the idea of a menu of health needs that may need to be addressed and patients should be directed to services they individually require. It is the GDG opinion that a tailored approach is cost-effective (i.e. offer only the rehabilitation components that are required rather than a comprehensive programme)." We found the above quotation rather disturbing. The focus of menu-driven care is informed patient choice, as choice can improve uptake and adherence to cardiac rehabilitation [3]. Therefore to suggest that "only the rehabilitation components that are required RATHER than a comprehensive programme" suggests that health	Thank you for your comment. The GDG did not consider the evidence available indicated benefit for patients with stable angina from comprehensive rehabilitation programmes. The GDG did not specify or address how individual components should be delivered and would agree that where possible choice is available for patients in how they access the aspects of support they require.

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						professionals are making the choice for patients without having a full menu available. This not only reduces the control that they have over their condition (so reducing self-management skills) but also removes the option of a comprehensive programme from people with angina, some of whom may find a full programme more suitable to their needs. In order to provide a full menu of options from which the patient can choose, there is a need for a choice of comprehensive programmes which can be delivered in various settings most suitable to patient needs (e.g. clinic, hospital, community, home), as home-based programmes are as effective as centre-based for people with CHD [4].	

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SH	British Association for Cardiovascular Prevention and Rehabilitation	4	Full	360		**"Assess the person's need for lifestyle adv example about exercise, stopping smoking weight control) and psychological support interventions as necessary.** **Address personal issues including:** • **self-management skills such as pac and goal setting** • dealing with stress or depression • **advice about physical exertion inclu activity."** On page 360, the GDG recommend a lifestyle assessment as well as provision of support for healthy lifestyle change including self-management skills, pacing and goal setting and addressing psychosocial ill-health. Primary care does not currently have the structure or skill base to provide these essential elements. An exercise referral scheme will address the physical activity component but not the other lifestyle/psychosocial aspects. Howe ver, all of these components are intrinsic to a comprehensive cardiac rehabilitation programme as outlined by patient-care pathway in the Department of Health Commissioning Pack for Cardiac Rehabilitation [2]. Therefore not to	Thank you for your comment. The remit for this guideline is Stable Angina. The evidence review did not find convincing evidence for the benefit of comprehensive rehabilitation programmes in patients with Stable Angina. The GDG is therefore not recommending such a programme for patients with Stable Angina. The GDG considered that individual patients would benefit from individual components of cardiac rehabilitation and this needs to assessed and addressed on an individual basis.

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						recommend cardiac rehabilitation programmes for patients with stable angina denies these patients this very effective comprehensive patient-care pathway that can meet the GDG's recommendations. In conclusion, BACPR would like reassurance that the GDG will revise this section of the guideline to reflect the modern evidence-based approach to prevention and rehabilitation in people with CVD. [1] British Association for Cardiac Rehabilitation. *Standards and Core Components for Cardiac Rehabilitation.* London, BACR. 2007. [2] Department of Health. *Cardiac Rehabilitation Commissioning Pack: Service specification for cardiac rehabilitation services.* London, Department of Health. 2010. [3] Dalal et al. Home based cardiac rehab and outcomes. (Letter) BMJ. 2009;338: 1160 [4] Dalal et al. Home based versus centre based cardiac rehabilitation: Cochrane systematic review and meta-analysis. BMJ 2010;340:b5631. doi:10.1136/bmj.b5631	

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SH	British Cardiovascular Intervention Society BCIS	1	Full	324	2	We strongly disagree with recommendation **"Do not routinely perform functional tests for myocardial ischaemia or anatomical tests for obstructive coronary artery disease to stratify risk.** **Comment:** When managing patients with stable angina, a key question for cardiologists is when to undertake angiography with a view to revascularisation rather than continue anti-anginal drugs alone. While we agree that failure to control symptoms with drugs is a reasonable indication for revascularisation, we know from abundant trial evidence that patients with extensive coronary artery disease (left main stem lesions and 3 vessel disease for example), reflected by extensive ischaemia on non-invasive testing, have a worse prognosis than those with more limited disease. The earlier trials of bypass grafting versus medical therapy alone showed a clear prognostic benefit for certain subsets of patients. Moreover they taught us that lower risk patients do not need to be considered for revascularisation unless deemed appropriate for symptomatic benefit. Although the more recent COURAGE and BARI-2D trials have not shown prognostic benefit for select groups of low risk patients who could have been	Thank you for your comment. The recommendation has been revised following stakeholder comment. We now include a consensus recommendation to consider anatomical or functional testing in people whose symptoms are controlled by medical therapy. We agree that patients with extensive coronary artery disease and extensive ischaemia have a worse prognosis, but we found no adequate evidence that revascularisation on the basis of ischaemia alone improves outcome. We also agree that earlier trials of CABG versus medical therapy demonstrated survival benefit for surgically treated patients, but several important limitations restrict the relevance of this evidence to contemporary practice. For example, in the Yusuf meta-analysis the patients were predominantly middle aged men and the results do not necessarily apply to all patients considered for CABG in contemporary practice. Only 150 patients had left main stem disease. The magnitude of benefit in absolute terms also needs to be considered. Among patients with an abnormal exercise treadmill test (indication of ischaemia)

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						treated by either medical therapy or revascularisation, the findings of these trials are not sufficient to suggest that patients do not need risk stratification. Older trials of CABG vs. medical therapy (Yusuf S Lancet 1994:344;563-70) showed that patients with LMS or severe multi-vessel disease, particularly in the context of LV dysfunction, gain prognostic benefit from revascularisation regardless of symptoms. Subsequent studies of PCI vs CABG have shown that the method of revascularisation does not appear to be of importance with respect to survival for all but a few very patients with severe disease who may benefit from CABG more than PCI (latest as yet unpublished results of the SYNTAX trial). All of these studies reinforce the paradigm of care that patients should be risk assessed and that both coronary anatomy and the extent of ischaemia are important considerations in selecting patients for revascularisation. A method of identifying these high-risk groups is therefore required. Undertaking coronary angiography in all patients with stable angina is one possible approach but there is also strong evidence that such patients can be identified non-invasively. Numerous studies exist which	survival was extended by mean of 1.8 months over 10 years relative to patients with a normal exercise test and the interaction test for this difference was not statistically significant. Analysis of the interaction between baseline ejection fraction (as a continuous variable) and survival benefit at 5 years did not indicate any influence of left ventricular function on treatment effect. The SWISSI II trial enrolled patients with recent myocardial infarction and falls outside the scope of this guideline. The ACIP trial was included in the evidence reviews. ACIP was a pilot study and although it reported a prognostic advantage for revascularisation this benefit is based on a very small number of events. Moreover, the medical therapy in ACIP was sub-optimal by contemporary standards. The GDG considered that ACIP does not provide definitive evidence of a prognostic advantage of ischaemia-driven or revascularisation strategies, particularly when considered in the context of other contemporary and more powerful trials (e.g. COURAGE, BARDI-2D)

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						have been discussed in the draft guidelines but one more recent study provides further information. In over 13,000 patients studied by perfusion imaging and followed up for over 8 years, it was demonstrated that the beneficial effects of revascularisation were closely related to the extent of ischaemia. (Hachamovich et al. EHJ 2011 doi:10.1093) The severity of angina symptoms and the response of angina to medical therapy provide no information on the extent or severity of coronary artery disease. Therefore even careful follow up using symptomatic status alone, will not identify those patients with a poor prognosis who would gain prognostic benefit from revascularisation. Trials such as ACIP (Circulation 1997;95:2037) and Swiss II (JAMA 2007;297:1985–91) have shown significant prognostic benefit from revascularisation for patients with extensive but silent ischaemia. We suggest that the main COURAGE trial informs the debate poorly, because all patients had undergone coronary angiography prior to a decision to randomise, and the high risk cohort that are the focus of this discussion were excluded (only 6% of those screened were	We agree that COURAGE excluded high risk patients and that the patients represent a selected subgroup of all patients considered for revascularisation (this applies to all randomised trials, including the original trials of CABG versus medical therapy, as well as more recent and influential trials such as SYNTAX and MASS II). The GDG do not agree that the substudy of COURAGE provides adequate evidence to recommend revascularisation on the basis of ischaemia. The COURAGE nuclear substudy is underpowered. Moreover, the treatment groups in the substudy were not determined by randomisation. The substudy demonstrated greater reduction in ischaemia with PCI than with OMT by univariate analysis, but no appropriate multivariate analysis was presented. Follow-up myocardial perfusion scans were carried out after 6-18 months but no information is provided on the timing of the scans in the two groups. Reduction in myocardial ischaemia in either treatment group, i.e. medical treatment or PCI was associated with lower rates of death or myocardial infarction after univariate but not multivariate analysis. Moreover,

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						randomized). The nuclear sub-study of COURAGE did however provide evidence that even having excluded the highest risk patients, those with more extensive coronary artery disease and ischaemia gained prognostic benefit from revascularisation. It is the combination of a wide range of studies over many years and biological plausibility that leads the majority of UK cardiologists to be persuaded that risk stratification to identify those patients with extensive coronary artery disease is required as part of routine clinical practice. This allows patients with extensive coronary artery disease and a poor prognosis on medical therapy to be identified in order that they may be offered investigation by angiography and (if extensive disease is confirmed) treatment with revascularisation that confers a survival benefit. This method of managing patients with stable angina is a fundamental part of the current European Society of Cardiology Guidelines which recommend that following diagnostic testing, all patients undergo risk stratification tests (nuclear perfusion imaging, stress echo, stress or perfusion CMR or coronary angiography). These guidelines have been endorsed by both the	procedure related myocardial infarction was not included in the analysis, creating a bias in favour of PCI. The GDG concluded that the COURAGE nuclear substudy is hypothesis generating but does not provide definitive evidence on which recommendations can be based. We agree that any prognostic benefit of CABG may not be negated by the effects of optimal medical therapy but it is also be inappropriate to assume that the benefits of CABG and optimal medical therapy are additive. We agree that the results of trials in low risk patients cannot be generalised to all patients undergoing revascularisation procedures. We agree that compliance with medications in clinical practice may be less good than in randomised trials. This applies to antianginal and secondary prevention drugs, but also to drugs aimed at improving the long-term results of revascularisation procedures (e.g. thienopyridines). The GDG were aware that established cardiological practice includes risk

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						BCS and BCIS and are routinely followed by most UK cardiologists. The suggested NICE guidance would result in cardiologists managing patients with minimal angina but undiagnosed severe coronary artery disease and a poor prognosis with medical therapy alone. Risk stratification tests are widely available in the UK and we feel it would be inappropriate for cardiologists not to take advantage of the prognostic information that is easily provided by such tests. A further advantage of this approach is that patients identified as 'low risk' can be safely managed with medical therapy saving both the risk and expense of invasive investigation. The full draft guidance document seems to suggest that, although there is evidence that prognosis is related to extent of ischaemia, there are insufficient studies to provide clear evidence that reduction of ischaemia improves prognosis. In addition, it is suggested that new "optimal" medical therapy improves prognosis and that older studies are no longer relevant. This is one, extreme, interpretation of the available data but there are different interpretations of the same data and it is inappropriate to make firm recommendations when there is	stratification of patients with stable angina. The GGD considered that offering a test for ischaemia to every patient would incur considerable costs with uncertain risks and benefits; this might not be the best use of NHS resources.

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						considerable debate about the impact of isolated trials. For example, "optimal" medical therapy would have been applied to both arms of randomised studies had it been available, and we cannot conclude that the benefits provided by a reduction in ischaemia would have been negated by new methods of plaque stabilisation. Secondly, results of trials of a relatively low-risk cohort of patients cannot be applied to the totality of patients seen in clinical practice. Thirdly, the recommendation ignores the fact that compliance with multiple medications over a lifetime in day-to-day practice is considerably poorer than in the trials. Fourthly, although new trials are being designed to address this further, this does not mean that we should reject 30 years of clinical trial experience. It is somewhat extreme to state that "the relevance of their findings to contemporary practice is doubtful". We do not believe that NICE has adequately evaluated the different risk profiles of the patients entered in to the multiple trials performed over many years, nor determined the rate of exclusion from trials from those patients screened, nor fully evaluated the sub-group analyses of trials that have influenced current practice. If	

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						anything it seems to have been somewhat selective in determining which sub-group analyses to use when making recommendations. These trials have reinforced the beliefs of cardiologists that many patients who are at low risk of adverse cardiovascular events do not routinely need to be considered for revascularisation, but results also reinforce the current paradigm that high risk patients should be offered revascularisation. Although new trials have raised the debate about what level of risk should trigger a decision about revascularisation, and new trials are being proposed to answer this, it is a step too far to state that revascularisation never has a prognostic benefit. The guidance as it currently stands runs the risk of increasing the mortality associated with coronary disease in the UK.	
SH	British Cardiovascular Intervention Society BCIS	2	Full	255	2	We disagree with the statement **Consider CABG in preference to PCI for people with multi-vessel disease who have continuing symptoms despite optimal medical treatment and who: are over 65 years and/or have diabetes.** **Comment:** The sub-group analyses that have been evaluated by the NICE group to make the	Thank your for your comment. We agree that the wording of the recommendation did not convey our intention and have changed the wording of the recommendation. In NICE terminology the word 'consider' does not suggest that the preferred treatment should be used for all patients.

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						recommendation that CABG is preferable to PCI in those aged 65 or older, and/or in those with diabetes is not supported by the totality of evidence. The Hlatky meta-analysis, as with all meta-analyses, has flaws. Such a meta-analysis can only reflect evidence on the relatively low risk patients that have been included in the trials, it does not differentiate between trials of contemporary practice and trials of earlier forms of revascularisation, and it does not include all contemporary evidence regarding the various subsets. Age and diabetes should certainly influence decisions but they cannot by themselves dictate them.	
SH	British Cardiovascular Intervention Society BCIS	3	Full	278	2	We disagree with the statement **Do not offer angiotensing-converting enzyme (ACE) inhibitors to manage stable angina. Offer ACE inhibitors to treat other conditions, as appropriate.** **Comment:** It is confusing for NICE to discuss optimal medical therapy (to include statins and ACE-inhibitors) in its discussion on the relevance of revascularisation in contemporary practice and then to suggest that ACE-inhibitors are not required. The inclusion and exclusion criteria of the HOPE, EUROPA and PEACE trials should be evaluated to determine which patients should be considered for the benefits of	Thank you for your comment. Following stakeholder comment we reviewed this evidence review and the evidence included. We have now included the HOPE trial in our evidence review for ACE inhibitors. The EUROPA trial is excluded from our review as the study included 81% patients with no angina. The recommendations for ACE inhibitors have been revised following additional evidence from the HOPE trial.

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						these drugs. Although it is agreed that an ACE-I is not given to improve "angina" this class of drug is an effective secondary preventive agent in coronary artery disease but these guidelines suggest they are not needed for patients with angina. This recommendation flies in the face of internationally agreed clinical guidelines.	
SH	British Cardiovascular Intervention Society BCIS	4	Full	260	35	We are unhappy that the following statements are accurate: **The purpose of revascularisation is to improve the symptoms of stable angina.** **PCI and CABG are effective in relieving symptoms.** **CABG is slightly more effective than PCI in relieving symptoms of stable angina in the longer term.** **Repeat revascularisation may be necessary after either PCI or CABG and the rate is higher after PCI than CABG.** **Stroke is uncommon after either PCI or CABG, and the incidence is similar between the two procedures.** **Comment:** As discussed above, we are confident that many patient subgroups gain prognostic benefit from revascularisation.	Thank you for your comment. We accept that the wording of the recommendations at consultation was open to misinterpretation. The recommendations and advice to patients refer to situations where both procedures are options and were not intended to be applicable to all-comers. We have amended the wording to clarify this. We accept that CABG has been shown to confer a prognostic benefit in subgroups of predominantly middle aged men with stable coronary artery disease. The magnitude of this benefit in contemporary practice has not been defined, but we have amended the recommendations to take account of this potential survival advantage. We agree that the statement regarding the longer term anti-anginal efficacy of the

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						Although many studies show that more patients get more effective relief from angina in the short-to-medium-term, this is not true over 10 years (indeed NICE reviews the evidence on this in the full guidance) – angina status is equivalent at this time, partly because of the progression of vein graft disease in the CABG group and repeat revascularisation rates being higher in the PCI group. However, this is much less of an issue nowadays compared with the earlier trials because of the increased use of drug-eluting stents. The last issue relating to stroke is contentious and under those circumstances should either be deleted or re-worded. Although the stroke rates have not been statistically different in some of the PCI vs CABG trials, these results only apply to the relatively low risk patients that have been included in these trials, and this result cannot be applied to all-comers. The recent SYNTAX trial shows that in more complex subsets of patients the stroke rate is higher for CABG. It is well recognised that certain patients with extensive peripheral and cerebrovascular disease have a higher risk of stroke at the time of surgery and some multidisciplinary teams favour PCI as an approach for certain patients on this basis.	two revascularisation procedures was potentially misleading and the statement has been removed. The GDG agree that patients with extensive vascular disease may be at higher risk of stroke during revascularisation procedures, and that SYNTAX reported a higher stroke rate in the CABG group at one year. The GDG were concerned that diagnostic criteria for stroke vary between the clinical trials and may be applied differently between patients treated by CABG or PCI. In SYNTAX a diagnosis of stroke was made on clinical grounds and did not require confirmation by cranial imaging. There is uncertainty about the long term significance of stroke after myocardial revascularisation, and the experience of GDG members is that such strokes often do not result in major or permanent disability. The absolute numbers of strokes reported in the randomised trials is small and in the evidence review conducted for this guideline there was a significant difference between PCI and CABG for stroke at early follow-up but no significant difference at longer term follow-up. The GDG was not convinced that there is robust evidence for a

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						The recommendation therefore cannot be applied to all-comers being considered for revascularisation.	clinically important difference in stroke rate between the two revascularisation strategies. The GDG were also aware that patients are most interested in longer term permanent disability.
SH	British Cardiovascular Intervention Society BCIS	5	Full	204	28	We disagree with the statement **Do not routinely offer percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) to people whose symptoms are controlled with drug treatment.** As we have discussed above in the section on routine use of functional and anatomical testing we are strongly of the opinion that for patients with extensive disease (3 vessel or LMS lesions), it is reasonable to offer revascularisation even if symptoms are modest and respond well to medical therapy.	Thank you for your comment. This recommendation has been revised following stakeholder comment.
SH	British Cardiovascular Intervention Society BCIS	6	Full	General		**3. BCIS recommendations** We suggest that the statement **"Do not routinely perform functional tests for myocardial ischaemia or anatomical tests for obstructive coronary artery disease to stratify risk"** should be deleted and replaced by **"Do not rely on symptom control to assess prognosis and need for revascularisation. For those patients in whom diagnostic testing has not**	Thank you for your comment. The recommendations for use of functional testing have changed following stakeholder comment. The recommendations now state that patients whose symptoms are not satisfactorily controlled on optimal medical treatment should be considered for angiography. Patients whose symptoms are controlled on medical treatment should be

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						provided risk stratification information and for whom revascularisation might be appropriate, arrange risk stratification testing and offer coronary angiography and possible revascularisation to those with evidence of extensive ischaemia". We suggest that the statement **"Do not routinely offer percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) to people whose symptoms are controlled with drug treatment. [1.2.4]"** should be deleted and replace by **"In people whose symptoms are well controlled by medical therapy offer revascularisation only to those with evidence of extensive ischaemia or anatomically severe coronary artery disease".** We suggest that the **statement "Consider CABG in preference to PCI for people with multi-vessel disease who have continuing symptoms despite optimal medical treatment and who:** **are over 65 years and/or have diabetes. [1.4.10]"** should be deleted and replaced by **"When revascularisation is being recommended the choice of PCI or CABG should depend on clinical factors such as age, diabetes and other co-**	considered for functional or anatomical testing after discussion of the implications of investigation. The GDG has now made a consensus recommendation supporting revascularisation in this group if they are subsequently found to have severe coronary artery disease. The GDG do not agree that there is sufficient evidence to recommend revascularisation on the basis of ischaemia for patients with stable angina. The clinical reviews and health economics indicated that PCI is more cost effective than CABG when both are suitable but that there may be prognostic gain for some subgroups according to age and diabetic status. We have changed the wording of the recommendations to clarify that these recommendations are about patients who are considered suitable for either form of revascularisation. The GDG discussed the wording of the information for patients (Rec 1.4.12 in version for consultation) and reviewed the results from the evidence reviews to inform this. Using the more recent trials where stents and drug eluting stents are used they considered the absolute difference to be low and it was more

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						morbidities as well as the extent and complexity of coronary disease". This is equivalent to recommendation to 1.4.7 and it could be argued that the specific recommendations 1.4.8 – 1.4.10 could all be deleted and allow clinicians and MDTs to determine the best therapy for individual patients. We suggest a rewording of recommendations in 1.4.12 to: **"CABG is slightly more effective in relieving symptoms of stable angina in the short- to medium- term but an initial decision to perform PCI results in an equivalent angina status in the longer-term".** ..and **"Stroke is uncommon after either PCI or CABG and in many patients the incidence is similar between the two procedures, but in patients with more extensive disease, the risk of stroke is slightly higher with CABG".**	appropriate to inform patients that both are effective at relieving symptoms. The GDG considered that the evidence for stroke varied according to time point and that the significance of stroke (disabling or non-disabling) was not reported. In the Hlatky IPD meta-analysis the absolute numbers at 90 days were 12/2269 (0.5%) in PCI and 26/2268(1.1%) in CABG groups. The GDG consensus was that peri-procedural events were often minor and resolved and that patients were most interested in longer term permanent disability.
SH	British Cardiovascular Society	1	Nice	14	1.2.4	*Do not routinely offer percutaneous coronary intervention (PCI) or coronary artery 13 bypass grafting (CABG) to people whose symptoms are controlled with drug treatment. 14 (1.2.4)*	Thank you for your comments. 1. The recommendations for anti-anginal drug treatment are intended to ensure that patients receive evidence based care and that patients are not given trials of

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						1. The evidence presented suggests that medical treatment alone, whether anti-anginal medication is used singly or in combination, reduces the frequency of angina attacks and may improve exercise capacity compared to placebo in those with stable angina. There are few data on the proportion of patients that are rendered asymptomatic. Clearly, the re-alignment of emphasis on first-line medical therapy is important but there are many patients who continue to suffer intermittent symptoms despite medical therapy. This means that this section of the guideline is restricted in practice. 2. Percutaneous and surgical revascularisation consistently delivers earlier and more complete symptom resolution in a larger proportion of patients. This raises two points: (a) Firstly, it is well established that patient compliance falls with each drug addition and the number of drug doses to be taken. While medical therapy may be a reasonable first stage, there is a balance to consider between continued use of medical therapy to minimise symptoms and the need to continue medication for secondary prevention. Revascularisation consistently delivers improvement in angina symptoms	several drugs for which there is no evidence in combination before consideration for angiography. 2a. Quality of life was assessed in a study included in our economic review (Weintraub et al. 2008, based on the COURAGE trial) comparing PCI to medical treatment; PCI was associated with an overall QALY gain but the same study concluded that PCI was not cost-effective compared to medical treatment (i.e. the QALY gain did not justify the higher costs). 2b. We disagree that the benefits of statins and CABG are likely to be additive, and it is equally possible that the prognostic benefits of CABG will be partially or completely negated by the effects of statins. The GDG considered that further randomised trials are required to fully evaluate the role of revascularisation strategies in the contemporary era. 2 (b) and 3. Following stakeholder comment we have altered the recommendations for people whose symptoms are controlled on medical treatment to assess whether they have

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						compared to medical therapy and reduces the number/dose requirements for anti-anginal drugs. Although revascularisation cannot guarantee better prognosis free of death and recurrent MI, the simple reduction in need for (anti-anginal) medication consequent on intervention may well improve quality of life in a way not measured by the studies done to-date. (b) Secondly, this leaves the patient to focus on taking fewer tablets for secondary prevention alone. As the surgical studies for those with proximal LMS and 3VD were performed before optimal medical therapy, it is not known whether revascularisation plus optimal medical therapy versus optimal medical therapy alone would deliver prognostic benefit. It is not enough to state that the prognostic benefits of statin therapy are equivalent in scale to those delivered in the early surgical trials, as these benefits are likely to be additive - particularly in those with higher risk disease. Patients with LMS disease were excluded from Courage, so this aspect has not been tested. 3. Current guidelines, albeit based on old evidence and with all the limitations inherent, continue to support revascularisation for LMS and severe proximal 3VD in preference to continued	anatomically complex disease.

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						medical therapy. Patients with LMS and severe proximal 3VD have a worse prognosis. Introduction of anti-anginal medication without further non-invasive risk stratification limits the opportunity for the Cardiologist to identify these groups of patients at higher risk and to select them for invasive investigation and treatment. Courage did not alter this practice, certainly for LMS disease. Comment: On these grounds, the guideline might suggest: 'Do not routinely offer percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) to people whose symptoms are controlled with drug treatment and who do not have evidence of extensive ischaemia on non-invasive testing.'	
SH	British Cardiovascular Society	2	Nice		1.2.3	*Do not routinely perform functional tests for myocardial ischaemia or anatomical tests for obstructive coronary artery disease to stratify risk. (1.2.3)* The evidence is accepted in the document that functional testing offers additional prognostic information beyond that provide by clinical variables. The guideline does not support the use of functional testing in stable angina because there is a lack of	Thank you for your comment. The recommendation has been revised following stakeholder comment. We now include a consensus recommendation to consider anatomical or functional testing in people whose symptoms are controlled by medical therapy. The GDG recognises that the COURAGE nuclear substudy and registry data of Hachamovitch are influential in

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						evidence that acting upon that information makes a clinical difference to the patient. The two major studies in this area, the Nuclear Sub-study of Courage (Shaw 2008) and the registry data of Hachamovitch (2003), are dismissed by the writing group, yet they are influential within Cardiology. The study by Hachamovich has been extended to demonstrate that the beneficial effect of revascularisation is restricted to those with ischaemia and excludes those with scar (EHJ 2011). This confirmed the absence of effect on those with scar but no ischaemia post-MI (Erne JAMA 2007). The added benefit of functional imaging data are consistent with interventional studies that support the use of functional testing during angiography to improve outcomes from PCI – hence, assessment of fractional flow reserve identifies a population who do better with targeted PCI than those without such measurement (Tonin NEJM 2009). Many patients will have had functional testing as part of their work-up through their presentation with chest pain – in those who have mild, continued symptoms, it will be very difficult to ignore the results of those functional tests when they identify those	cardiology, but did not consider that either of these studies provides definitive evidence to support revascularisation on the basis of ischaemia alone. The COURAGE nuclear substudy is underpowered. Moreover, the treatment groups in the substudy were not determined by randomisation. The substudy demonstrated greater reduction in ischaemia with PCI than with OMT by univariate analysis, but no appropriate multivariate analysis was presented. Follow-up myocardial perfusion scans were carried out after 6-18 months but no information is provided on the timing of the scans in the two groups. Reduction in myocardial ischaemia in either treatment group i.e. medical treatment or PCI was associated with lower rates of death or myocardial infarction after univariate but not multivariate analysis. Moreover, procedure related myocardial infarction was not included in the analysis, creating a bias in favour of PCI. The GDG concluded that the COURAGE nuclear substudy is hypothesis generating but does not provide definitive evidence on which recommendations can be based. The Hachamovitch registry data were

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						with an adverse prognosis. A patient in clinic, diagnosed with angina, stable symptoms but occasional chest pain with reversibility of more than 5 segments/>10% myocardial mass or transient ischaemic dilatation who will not be referred for further invasive investigation? Comment: On these grounds, the guideline might suggest: 'Functional tests should be routinely performed for myocardial ischaemia to stratify risk.'	analysed with multivariate modelling and adjustment for non-randomised treatment assignment with a propensity score. Nevertheless, it is likely that patients with unmeasured comorbidities would have preferentially been treated by medical therapy, and this may contribute to the survival benefit reported after revascularisation. The GDG therefore considered these data to be exploratory and hypothesis-generating but they do not provide definitive evidence of a prognostic benefit in people with ischaemia. The GGD considered that offering a test for ischaemia to every patient would incur considerable costs with uncertain risks and benefits; this might not be the best use of NHS resources.
SH	British Cardiovascular Society	3	Nice			Minor Points: 1. Abbreviations: MPI is listed twice. PET is listed twice, with the only difference in the interpretation the presence of '–'.	Thank you for your comment. We think this comment is referring to the abbreviations in the Full version and we have reviewed this to remove repetition.
SH	British Cardiovascular Society	4	Nice		1.2.3 1.2.4	There is a lot of sense in this Guideline, not least a re-emphasis of medication as first-line treatment, with revascularisation being reserved mainly for patients with persistent angina. However, I am very uncomfortable with recommendations 1.2.3 and 1.2.4: "*1.2.3 Do not routinely perform functional tests for myocardial ischaemia or*	Thank you for your comment. The recommendations have been revised following stakeholder comment. We now include a consensus recommendation to consider anatomical or functional testing in people whose symptoms are controlled by medical therapy.

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						anatomical tests for obstructive coronary artery disease to stratify risk. *1.2.4 Do not routinely offer percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) to people whose symptoms are controlled with drug treatment.*" (1) The evaluation of studies looking at imaging and prognosis was limited to only those where >60% of patients had "stable angina". This excluded some very large studies from the nuclear literature (particularly those from Cedars-Sinai, where typically 35% of patients had angina), which universally show an increase in risk with increasing amounts of ischaemia. MPS has been shown to have prognostic value in every population in whom it has been evaluated (women, the elderly, different races, the obese, renal failure, prior to noncardiac surgery, post MI, post PCI, post CABG). Is it really credible that the predictive value of MPS (or for that matter stress echo) would cease to apply in the specific population defined by the Committee? Taking the Committee's approach a step further, every single one of the studies in the literature should actually have been excluded (!) on the grounds that, to my knowledge: (1) not one has looked	We agree that patients with ischaemia on functional imaging have a worse prognosis, but we found no evidence that revascularisation on the basis of ischaemia alone improves outcome. The GDG view on the COURAGE nuclear sub study and Hachamovitch et al analysis are outlined in our response to previous comment from same stakeholder about these recommendations. All registry studies are potentially confounded by imbalances in patient characteristics between non-randomised groups.

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						specifically at patients with stable angina that has resolved on medical management; (2) most will have studied patients off antianginal medication (particularly beta-blockers) to improve diagnostic sensitivity, whereas the Committee would want to know about prognosis on medication. (2) For these recommendations to be valid, we need to be confident that patients with severe multivessel coronary disease and/or extensive inducible ischaemia, whose symptoms have settled on one or two antianginal drugs, derive no prognostic benefit from revascularisation compared with optimal medical therapy. There would therefore be no logic in routinely looking for such patterns of disease as revascularisation would not be indicated. Whilst there has never been a RCT, the Committee are aware of the evidence in the literature from various registries to support the idea that, whilst revascularisation does not confer prognostic benefit over medical management in all-comers with CAD, there are angiographic and functional subsets of patients who may benefit. For example, just focussing on functional assessment: Weiner DA *et al*. Value of exercise testing in determining the risk classification and the	

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						response to coronary artery bypass grafting in three-vessel coronary artery disease: A report from the Coronary Artery Surgery Study (CASS) Registry. *Am J Cardiol* 1987; **60:** 262-6. Hachamovitch R *et al*. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation* 2003; **107:** 2900-6. Of direct relevance is the COURAGE Nuclear Substudy, the findings of which are summarised in 4.2 of the Guideline: PCI is more effective in treating ischaemia than medication, whilst reduction of ischaemia leads to a better outcome. It is also worth considering the FAME Study. This used an albeit invasive assessment of the functional significance of coronary stenoses, but nevertheless showed that a PCI strategy guided by function led to fewer cardiac events than one guided purely by angiographic appearances. There is therefore a strong suspicion that PCI might confer prognostic benefit over medical management in the subset of patients with significant inducible ischaemia (however assessed).	

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						These concepts are so much part of the fabric of clinical cardiology that, despite the Committee's well-intentioned suggestion in 4.3 for a RCT, I doubt that many (any?) cardiologists would be happy to randomise real-life patients with severe LMS or proximal 3 vessel CAD, whether asymptomatic or not. Lack of (RCT) evidence of benefit does not prove that there is a lack of benefit. It is one thing for NICE to use a strict "Evidence Based Medicine" approach to restrict introduction of a novel drug or technology. However, when the intention is to overturn almost universal practice it cannot enough to point to a lack of RCTs: first there ought to be high quality evidence that current literature-backed practice is actually wrong. (3) The majority of patients, assuming that they have been "processed" according to the Investigation Guideline 95, will already have undergone an imaging investigation as their first-line diagnostic procedure, which must have been abnormal for the Management Guideline to apply. There is a paradoxical contrast between a rather aggressive investigational algorithm, and a very conservative treatment algorithm. [More paradoxical still, the only group which	

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						will not have had any form of imaging will be the highest risk group of all, *i.e.* those with >90% probability of obstructive CAD.] As the information will already be available, recommendation 1.2.3 will seldom be an issue in practice, but cardiologists will not infrequently be faced with patients shown to have multivessel CAD on CT / invasive angiography, or extensive ischaemia on functional imaging. I find it very hard to believe that cardiology colleagues on the Committee, faced with a worried patient with tight left mainstem stenosis or very extensive ischaemia, would be happy to leave them unrevascularised even if their angina had settled on medication! I would like to see these Recommendations reworded as follows: "*1.2.3 A functional test for myocardial ischaemia or an anatomical test for obstructive coronary artery disease should usually be performed to stratify risk."* *1.2.4 Do not routinely offer percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) to people whose symptoms are controlled with drug treatment, unless high-risk features are present on functional or anatomical testing.*"	

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SH	British Cardiovascular Society	5	Nice	general		GENERAL COMMENT FROM BCS (Dr Adrian Brady): The BCS welcomes this directive and guidance on the management of patients with stable angina. The document is certainly long, running to over 450 pages. We have taken the opportunity to examine the new NICE Guidance in the setting of the current ESC Guideline, the current ACC/AHA Guideline, the SIGN 2007 Guideline on the management of stable angina, and the current NICE-BHS Guideline for the management of hypertension. There are certainly many valuable components of the NICE Guidance, in particular, the evidence for the different types of coronary heart disease, whether single, double or triple vessel is well explained. What is really missing from the Guidance, and which is prominent in every other published guideline, is some description of the physiology and pharmacology and mechanism of angina. This leads directly into the recommended therapy and there is universal acceptance that beta blockers are the best drugs for angina, but this does not	Thank you for your comment. A NICE guideline is not intended to cover the basic physiology and pathology of a condition. NICE guidelines aim to answer key clinical questions about a condition and these key areas are decided by the scoping process and consultation with stakeholders. The current NICE-BHS guidelines are being updated and are currently out for consultation. The consultation draft does not include a recommendation for B Blocker as choice of anti-hypertensive medication in patients with angina. The GDG wished to specifically examine evidence for which drug should be used as first line in patients with stable angina. The evidence reviewed comparing b blockers and calcium channel blockers did not did not indicate better outcomes with b blocker. The SIGN guideline states that benefit for beta blocker first line comes from their effect on patient post MI, and with heart failure.

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						seem to feature in the current NICE draft. This is certainly at odds with the current NICE Guidance of hypertension, where the presence of angina is a compelling indication for beta blocker prescription. Likewise, in the current SIGN Guideline, beta blockers are also first line therapy for patients with angina. This is exactly the same in the European Society of Cardiology Guideline and in the American College of Cardiology/American Heart Association Guideline. It is accepted national practice, really across the board, that cardiologists will start treatment for angina with a beta blocker. This is to reduce heart rate, as described in all the other guidelines except the current NICE draft. It is a recommendation of the BCS, unless there is good evidence that all the other current guidelines are incorrect in their interpretation of the data, that there is an explanation of the pathophysiology of myocardial ischaemia causing angina. It would not really be out of place to discuss cardiac work, heart rate, blood pressure demands and so on. While this might sound a little old fashioned, NICE Guidelines should be for education as well	

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						as information and if the document is really going to run to approaching 500 pages, there should certainly be space for a little description of fundamental physiology and pathology of angina.	
SH	British Hypertension Society	1	Full	General		The reviewers of the British Hypertension Society braced themselves for the 456 page report by NICE for the treatment of angina. Running to such length, we expected the guideline to be complete in every aspect of the background and management of angina pectoris. The BHS was surprised and rather disappointed that nowhere in the introductory chapters was there any description of basic physiology and pathology of coronary heart disease and the mechanisms of angina. We teach medical students that angina is caused by lack of oxygen, caused by an increase in cardiac demand, brought about by an increase in heart rate, blood pressure or both. These are fundamental cornerstones of cardiovascular medicine yet have been left out of the guidelines. The current NICE-BHS hypertension guidance clearly states beta blockers are the preferred first choice treatments for hypertension and angina because of a reduction in heart rate and blood pressure. It seems universal practice to lower these	Thank you for your comment. A NICE guideline is not intended to cover the basic physiology and pathology of a condition. NICE guidelines aim to answer key clinical questions about a condition and these key areas are decided by the scoping process and consultation with stakeholders. The current NICE-BHS guidelines are being updated and are currently out for consultation. The consultation draft does not include a recommendation for B Blocker as choice of anti-hypertensive medication in patients with angina. We will continue to liaise with NICE to ensure that we are aware of any changes to the hypertension guideline.

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						two readily quantifiable determinants of myocardial oxygen consumption and it is the BHS' view that among 456 pages of this guideline, there should be some space devoted to physiology and pathophysiology. Otherwise the detail on the different types of coronary heart disease and patterns of anatomy with appropriate intervention is very specialised and well written.	
SH	British Hypertension Society	2	Full	General		Another comment identified by senior reviewers within BHS was that the draft NICE angina guidance appears to give equal weight to dihydropyridine calcium channel blockers and beta blockers as treatments for angina, yet the general cornerstone of British cardiovascular practice is to lower heart rate with a beta blocker, or rate-limiting calcium channel blocker, ie Diltiazem or Verapamil. If the new NICE angina guidance is to go against such well established practice, some explanation should be given.	Thank you for your comment. The GDG did not use heart rate as an outcome as heart rate was considered a surrogate outcome and the outcomes chosen were related to angina morbidity and mortality. Evidence for the use of dihydropyridine CCBs in angina was found in the evidence reviews and these had similar efficacy to BBs.
SH	British Nuclear Cardiology Society (BNCS) & British Nuclear	1	Full	53	31	Patients will want to know their prognosis irrespective of treatment options. Functional testing is required for this. This guideline ignores the patient‟s right to be informed about their prognosis, even if there is no way of altering their clinical outcome. Suggest reword to: "1.2.3 A functional test	Thank you for your comment. This recommendation has now been changed. The GDG disagree that all patients want to know their prognosis irrespective of treatment options. This issue also did not arise in the evidence review of patient information. Offering a test to determine

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	Medicine Society (BNMS)					for myocardial ischaemia or an anatomical test for obstructive coronary artery disease should usually be performed to stratify risk."	prognosis for every patient would incur considerable costs but might not be a cost-effective use of NHS resources.
SH	British Nuclear Cardiology Society (BNCS) & British Nuclear Medicine Society (BNMS)	2	Full	54	1	High risk features on MPS have long been recognised. The nuclear substudy of COURAGE also demonstrated that ischaemia driven revascularisation resulted in lower MACE. Therefore suggest reword to: "*1.2.4 Do not routinely offer percutaneous coronary intervention (PCI) or coronary artery* *bypass grafting (CABG) to people whose symptoms are controlled with drug treatment,* *unless high-risk features are present on functional* *or anatomical testing.*"	The GDG agree the functional testing including myocardial perfusion imaging, can stratify risk. The GDG were not convinced that the presence of ischaemia during such testing identifies patients who gain prognostic benefit from revascularisation. The GDG considered that the COURAGE nuclear substudy is underpowered, and noted that the treatment groups were not determined by randomisation. The substudy demonstrated greater reduction in ischaemia with PCI than with OMT by univariate analysis, but no appropriate multivariate analysis was presented. Follow-up myocardial perfusion scans were carried out after 6-18 months but no information is provided on the timing of the scans in the two groups. Reduction in myocardial ischaemia in either treatment group was associated with lower rates of death or myocardial infarction after univariate but not multivariate analysis. Moreover, procedure related myocardial infarction was not included in the analysis, creating a bias in favour of PCI. The GDG concluded that the COURAGE nuclear

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							substudy is hypothesis generating but does not provide definitive evidence on which recommendations can be based. The GDG considered that further studies are required to determine whether ischaemia identifies patients who may gain prognostic benefit from revascularisation.
SH	British Nuclear Cardiology Society (BNCS) & British Nuclear Medicine Society (BNMS)	3	Full	319	20	Nine studies confirmed independent prognostic value of MPS. Studies encompassing tens of thousands of patients demonstrating independent prognostic value of MPS were excluded by the arbitrary ">60% stable angina" cut-off. This is not a reasonable assessment of the voluminous and far reaching evidence that MPS provides independent prognostic value in all comers and also in any particular subset (diabetes, women, elderly, ethnic minorities, post revascularisation, pre non-cardiac surgery and renal impairment).	Thank you for your comment. The remit for the guideline is stable angina and we are required to make recommendations for that group. The GDG agree that ischaemia on myocardial perfusion scanning is associated with poorer prognosis but did not find any robust evidence that intervening on the basis of ischaemia improved outcome.
SH	British Society of Cardiac Imaging	1	Full	326	21	Reference should be made to CT angiography as a preferred alternative to invasive coronary angiography in stable angina.	Thank you for your comment. The search conducted to look for incremental prognostic information in patients with stable angina did not find studies of CT angiography that met our inclusion criteria. Following stakeholder consultation we have now included a consensus recommendation to consider

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							functional or anatomical testing for people whose symptoms resolve on medical treatment.
SH	British Society of Cardiovascular Magnetic Resonance (BSCMR)	1	Full	53	31	The idea of **NOT** performing functional testing (as suggested in the proposed guidelines) to investigate CAD patients for ischaemia will be controversial. The majority of practicing cardiologists recognise that 'ischaemia' is a fundamental determinate of cardiovascular risk/outcome (e.g. arrhythmia, sudden cardiac death etc). However, whilst we all hold the concept that reducing ischemia is good and should improve outcomes, the actual data in the literature to support this hypothesis with respect to non-invasive imaging are admittedly scant. Indeed, whilst there is a wealth of evidence over decades of mechanistic research or using surrogate outcomes, we appreciate that there has never been a true randomised controlled trial (RCT) of this hypothesis. One could make the analogy that there has never been an RCT of skydiving to show that parachutes save lives, however common sense and expert opinion are believed! The COURAGE nuclear sub-study was admittedly underpowered, but is perhaps the best contemporary evidence available.	Thank you for your comment. The GDG agree that extent of ischaemia is associated with poor prognosis. The GDG agree that there is no adequate evidence to support the hypothesis that intervening on the basis of ischaemia alone improves outcomes. The GDG agree that the COURAGE nuclear substudy is underpowered. Moreover, the treatment groups in the substudy were not determined by randomisation. The substudy demonstrated greater reduction in ischaemia with PCI than with OMT by univariate analysis, but no appropriate multivariate analysis was presented. Follow-up myocardial perfusion scans were carried out after 6-18 months but no information is provided on the timing of the scans in the two groups. Reduction in myocardial ischaemia in either treatment group i.e medical treatment or PCI was associated with lower rates of death or myocardial infarction after univariate but not multivariate analysis. Moreover, procedure related myocardial infarction was not included in the analysis, creating

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						Their exploratory outcomes analysis suggested that the risk of death or MI rose and fell in tandem with the extent of residual ischemic myocardium at follow-up imaging. Compared with the 231 patients with a smaller reduction in ischemia, the 82 with an ischemia reduction >5% of myocardium had a 0.47 relative risk of death or MI (95% CI 0.23-0.95, p=0.037).	a bias in favour of PCI. The GDG concluded that the COURAGE nuclear substudy is hypothesis generating but does not provide definitive evidence on which recommendations can be based. The guideline recommends angiography for patients whose symptoms do not resolve on medical treatment as the feasibility of revascularisation is determined mainly by coronary anatomy. The GDG recognise that additional functional testing may be helpful in evaluating angiographic findings and this is included in the recommendation. Following stakeholder consultation the GDG have added a recommendation to consider testing in patients whose symptoms are controlled on optimal medical treatment.
SH	British Society of Cardiovascular Magnetic Resonance (BSCMR)	2	Full	53	31	We would further like to comment on the proposed draft guidelines' suggestion that [*This recommendation partially updates recommendation 1.2 of Myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction' (NICE technology appraisal guidance 73)]* TA073 recommendation 1.2 specifically	Thank you for your comment. Recommendation 1.2 of TA073 recommends the use of SPECT for patients who remain symptomatic following myocardial infarction or reperfusion interventions. The recommendations in this guideline refer to patients with stable angina and included those who have (and have not) had myocardial infarction or revascularisation.

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						stated "*MPS using SPECT is recommended as part of the Investigational strategy in the management of established CAD in people who remain symptomatic following myocardial infarction or reperfusion interventions.*" This current proposed draft guideline makes absolutely **NO** reference to the management of patients with previous MI or revascularisation. We believe that this is a major omission and that the guidelines are over simplistic. This group of patients (with previous MI or revascularisation) are often the most complex to manage and it can be fundamental to their management to assess for residual ischaemia and myocardial viability. Patients with a substantial amount of dysfunctional but viable myocardium are likely to benefit from myocardial revascularization and may show improvements in regional and global contractile function, symptoms, exercise capacity, and long-term prognosis [e.g. Allman KC, J Am Coll Cardiol 2002]. By omitting this very common clinical problem from the draft guidelines there is the real risk that this large group of CAD patients could be forgotten and disadvantaged.	We have not excluded people with stable angina who have had previous MI or revascularisation when searching for evidence. The scope of this guideline was stable angina and it does not cover all people with coronary artery disease.

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SH	British Society of Cardiovascular Magnetic Resonance (BSCMR)	3	Full	324		The highlighted recommendation "*Do not routinely perform functional tests for myocardial ischaemia or anatomical tests for obstructive coronary artery disease to stratify risk*" is **contradictory** to recently published international guidelines for myocardial revascularisation [The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS), EHJ 2010, 31:2501-2555]. We believe that as the same body of evidence would have been considered, it is inappropriate to produce UK guidelines that are out of step with the International guidelines. The disparity must arise from the fact that the CDG is principally concerned with the health economic evaluation (and saving money) which can be in conflict with clinical management guidelines which are patient focused. It is imperative that any new UK NICE guidelines have the support of practicing clinicians; sadly this has not always been the case in the recent past. It would be disappointing if these proposed guidelines for the management of stable angina were not amended at this stage, otherwise the risk is they will be ignored.	Thank you for your comment. The recommendation has been revised following stakeholder comment. NICE guidelines are developed by an independent Guideline Development Group according to NICE processes which include clinical effectiveness and cost effectiveness evidence. The GDG are not required to consider other guidelines in the review process. Health economics is incorporated into NICE guideline development with the aim of maximising health outcomes from available resources; the focus is on patients' health rather than on saving costs (more expensive options can be cost effective if they generate substantial health gain). The cost to the NHS of performing the test is not considered at this stage.
SH	Cordis	1	Full	gen		Cordis (Johnson & Johnson Medical Ltd)	Thank you for your comment.

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	(Johnson & Johnson Medical Ltd)					have no further comments	
SH	Department of Health	1	Full	52	11-15	Reference is made to practitioners not 'routinely' offering imaging tests to risk stratify patients, or to aid decisions about revascularisation for those whose symptoms are controlled on medical therapy. Whilst both of these are obviously discussed in detail in the body of the text, our concern is simply with the word 'routinely.' This seems to be so vague as to make the recommendations of limited value. This may be what the guideline authors aimed to achieve, allowing practitioners to do what they think is fitting for individual patients, but assuming that the recommendations were intended to be a little more prescriptive. We are not sure that this is achieved by the word 'routinely.' If the guideline development group (GDG) felt that undertaking imaging or performing revascularisation (for asymptomatic patients) should be the exception rather than the rule, then we consider that the word 'routinely' does not seem to convey their message. On the other hand, if they intended their guidance to support clinicians' decisions on an individual patient basis, then perhaps the words 'where	Thank you for your comment. Following stakeholder consultation we have altered the wording of this and other recommendations about testing to clarify the intention of the GDG.

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						clinically appropriate' could be substituted for 'routinely' Could you please give this some consideration. We are not certain that readers will understand what these two recommendations are intended to convey. On page 325, the Guideline Development Group's (GDG) intention is stated to be *'that functional and anatomical testing for prognostic information alone was unlikely to be justified or appropriate for the majority of patients.'* We would simply request the GDG to reconsider whether its intended message is adequately conveyed by the phrase *'do not routinely offer.'*	
SH	Department of Health	2	Full	52	25-28	As it stands, this seems to recommend PCI as the preferred revascularisation option for left main stem disease. In our view, this could be seen as contentious by both surgeons and some interventionists, because there are a variety of left main stem lesions, some of which are very suitable for PCI and others, which are unattractive. The caveat used *"and the anatomy is suitable for PCI"* appears to leave it open for the interventionist to decide alone whether the left main stem disease is suitable or not. Given the range of opinions at large in the	Thank you for your comment. Following stakeholder consultation we reviewed the recommendations regarding MDT meetings and choice of revascularisation strategy. We have changed the recommendations to clarify the meaning intended by the GDG. The recommendations now state that we would expect most people with LMS disease to be discussed at an MDT.

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						interventional community, we feel that this position is unsatisfactory, and we would prefer to see a recommendation that there will be a discussion between interventionist and surgeon whenever complex anatomy is found, before the choice of revascularisation strategy is recommended to the patient. After all, such a consensus recommendation to the patient will also have taken into account other factors, such as their co-morbidity and relative contraindications to PCI or CABG. We are concerned that recommendation 1.4.8 appears to give too much licence to interventionists to act as judge and jury more so than at present exists, because of the guideline's statement that PCI is *preferred* over CABG.	
SH	Department of Health	3	Full	52	29-31	Reference is made to the anatomy being 'unsuitable for PCI' but does not appear to state how (or by who) judging the anatomy's suitability should be made. Could you please consider making some reference to this after discussion between clinicians, and not just on the basis of a single surgeon or interventionist. We think that it is true that many - perhaps most - angiograms are fairly obviously either suitable or unsuitable for PCI, and an MDT	Thank you for your comment. Following stakeholder consultation we reviewed the recommendations regarding MDT meetings and choice of revascularisation strategy. We have altered the recommendation to indicate which patients the GDG considered should be discussed at MDT meetings **[updated recommendation no. 1.5.13]**. The GDG did not consider it practical or appropriate that all patients should be discussed at MDTs. The GDG recognised the issue of

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						is not required to determine this. However, where a patient's anatomy falls into the 'grey area' where both PCI and CABG might be an option, then we believe that a better (or at least a more defensible) decision would be made if a discussion between clinicians were to be recommended. If this was intended by the GDG we are not sure that the current recommendations, when taken in isolation, make this intention clear enough. Recommendation 1.4.6 (page 57, lines 5-8) appears to point towards a dialogue being preferred, but does not give any indication of when such a dialogue is appropriate. An aggressive interventionist who sees little value in CABG (and we believe that there are such people) may *consider* that there is rarely or never a need to discuss patient management with other interventionists (who may be more conservative), or a surgeon. If NICE is to recommend more dialogue between disciplines (which we would support) then we feel that it would be helpful if the circumstances in which such a dialogue should be undertaken were more clearly defined in the guideline recommendations.	aggressive interventionists but considered that this issue would more appropriately be dealt with by measures such as audits and case reviews in individual units.
SH	Department of Health	4	Full	50	1-3	It is made clear that if ivabradine is added to a calcium antagonist, then the calcium antagonist should be of a dihydropyridine variety, and not one that (presumably) has	Thank you for your comment. There is evidence for combination of BB with ivabradine.

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						negatively chronotropic properties (please see the footnote on page 55). On page 129 (paragraph 1) this footnote advice would seem to be because the manufacturers "do not recommend" ivabradine with non-dihydropyridine CCBs. The algorithm, on the other hand, does allow for the addition of ivabradine to a beta-blocker, which we feel the reader may find odd when its use is contra-indicated with an alternative negatively chronotropic agent. Could you please consider slightly expanding the footnote on page 55 to indicate why ivabradine should *not* be added to a rate limiting CCB, but *can* be added to a beta-blocker.	The following explanation for advice regarding the combination of ivabradine with non-dihydropyridine CCBs is taken from ivabradine SPC: Ivabradine is metabolised by CYP3A4 and it is a very weak inhibitor of this cytochrome. CYP3A4 inhibitors and inducers are liable to interact with ivabradine and influence its metabolism and pharmacokinetics to a clinically significant extent. Drug-drug interaction studies have established that CYP3A4 inhibitors increase ivabradine plasma concentrations. Increased plasma concentrations of ivabradine may be associated with the risk of excessive bradycardia. Specific interaction studies in healthy volunteers and patients have shown that the combination of ivabradine with the heart rate reducing agents diltiazem or verapamil resulted in an increase in ivabradine exposure and an additional heart rate reduction of 5 bpm. The concomitant use of ivabradine with these medicinal products is not recommended. It would not be usual to provide this level of detail with a recommendation or footnote but we have added this to the evidence to recommendations section.

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SH	Department of Health	5	Full	56	24-26	This appears to be rather confusing in that it states *"review the results of any functional and/or anatomical tests performed at diagnosis when revascularisation is being considered".* Could you please clarify why a functional or anatomical test is undertaken before a coronary angiogram relevant to decision making about the appropriateness of revascularisation, when the same test undertaken after an angiogram is implicitly discouraged by their recommendation 1.2.3 (see above)?. The potential for value being derived from these tests is also hinted at in their following recommendation 1.4.3 (page 56, lines 27-32).	Thank you for your comment. We have removed this recommendation following stakeholder comments. We have altered recommendations to make the place of testing clearer.
SH	Medtronic	1	Full	General		Many thanks to NICE for a well thought out guideline, Medtronic has no specific comments.	Thank you for your comment.
SH	National Refractory Angina Centre	1	Full	General		**Patient centred care** The GMC and the NMC have separately recommended patient centred care as an essential element of optimal healthcare practice, but we have not yet reached the position when patient centred care is widely practiced. NICE clearly has a responsibility to promote patient centred care and yet the term appears only once in the draft angina	Thank you for your comment. We agree with the importance of patient-centred care. Information on the patient centred care is included at the start of the NICE version of the guideline and will also be included in the Quick Reference Guide for healthcare professionals.

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						guidance document and then only in a footnote describing a questionnaire (p354). It may be that patient centredness is considered so central to angina management that the GDG thought it unnecessary to mention it. However, a formal acknowledgement of the importance of delivering patient (or person) centred care throughout management should be included, as appeared in CG48 p 5	
SH	National Refractory Angina Centre	2	Full	General		**Missing advice: Absence of placebo or sham controlled trial in palliative revascularisation.** It is pleasing that the GDG has acknowledged the importance of patient education and the particular advice to ensure patients understand that PCI in stable angina does not prevent heart attacks or prolong life. The GDG correctly acknowledges PCI for stable angina is for the relief of angina symptoms and claims that evidence shows PCI is effective. While it is the case that controlled trials have demonstrated that patients who receive PCI experience a significant, albeit temporary, improvement in symptoms, it is not clear what mechanism is	Thank you for your comment. The GDG discussed this issue during the development of the guideline and following the submission of comments. The GDG consider that placebo control is inappropriate and unethical when the clinically relevant question is not whether revascularization is better than nothing but whether it is better than standard treatment. To this end there have been multiple studies of PCI vs medical treatment in patients with angina which have confirmed the additional benefit of PCI for symptom relief. These trials have informed the guideline. While placebo control is a practical and readily applicable methodology in the evaluation of new drugs, it is more difficult to apply in the evaluation of procedures The GDG

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						responsible. Invariably whenever palliative interventions have been subjected to a placebo/sham controlled study a significant placebo effect has been observed. It is therefore likely that placebo plays a role in palliative PCI. It is an undeniable fact that the absence of such research makes it impossible to rule out with certainty the possibility that the observed improvement in symptoms following PCI is all or partly explained by a non-specific treatment effect (placebo). It is not consistent with NICE's position on scientific probity for the guidance to simply ignore the role of placebo in palliative revascularisation.	could not envisage what the placebo arm of a PCI trial would look like or whether "placebo" instrumentation of the coronary circulation would be ethically acceptable. The ethical argument centres around the excess procedural risk that patients in the placebo arm (potentially involving the insertion of catheters across tight coronary stenoses without balloon inflation or stent insertion) would be exposed to compared with those who received active treatment. Similarly it would be practically very difficult to conduct an unbiased sham-controlled study of a procedure that is carried out in fully conscious patients and it is unlikely that such a trial will ever be conducted. *REF: Ezekiel EJ, Miller FG. The ethics of placebo-controlled trials – a middle ground. NEJM 2001;345:915-9.*
SH	National Refractory Angina Centre	3	Full	26	10-15	**Placebo and patient autonomy** NICE has a responsibility to present a scientifically balanced argument for each therapy it considers, so that individual clinicians, commissioners and patients are able to come to a balanced judgement about the justifiability of treatments NICE deems appropriate in a particular condition. In its consideration of other angina	The GDG discussed this issue during the development of the guideline and following the submission of comments. The GDG consider that placebo control is inappropriate and unethical hen the clinically relevant question is not whether revascularization is better than nothing but whether it is better than standard treatment. To this end there have been multiple studies of PCI vs medical

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						treatments, including physical interventions that were ruled inappropriate, the DGD document makes over 100 references to "placebo" and another 20 to "sham." It is an indisputable fact that there is not a single piece of credible scientific research examining the effect of placebo in palliative PCI. Consequently placebo could explain all or part of the observed benefits of palliative PCI. The absence of a balanced discussion on the possible role of placebo prevents patients making informed decisions. This negates one of the primary objectives of the guideline.	treatment in patients with angina which have confirmed the additional benefit of PCI for symptom relief. These trials have informed the guideline. While placebo control is a practical and readily applicable methodology in the evaluation of new drugs, it is more difficult to apply in the evaluation of procedures The GDG could not envisage what the placebo arm of a PCI trial would look like or whether "placebo" instrumentation of the coronary circulation would be ethically acceptable. The ethical argument centres around the excess procedural risk that patients in the placebo arm (potentially involving the insertion of catheters across tight coronary stenoses without balloon inflation or stent insertion) would be exposed to compared with those who received active treatment. Similarly it would be practically very difficult to conduct an unbiased sham-controlled study of a procedure that is carried out in fully conscious patients and it is unlikely that such a trial will ever be conducted. We have included recommendations to ensure patients are given balaced information on the risk and benefits of procedures. REF: Ezekiel EJ, Miller FG. The ethics of

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							placebo-controlled trials – a middle ground. NEJM 2001;345:915-9.
SH	National Refractory Angina Centre	4	Nice	26	10-15	**Placebo and GP commissioning** An important role of NICE guidance is to assist healthcare practitioners to make complex decisions. It is scientifically (and economically) irresponsible to ignore the absence of a placebo/sham-controlled study of palliative PCI and present a one sided view of the evidence for PCI's "cost-effectiveness." By ignoring the possibility of a major placebo effect the proposed guidance undermines individual GPs' and GP commissioners' abilities to make rational choices with, and on behalf of their patients.	Thank you for your comment. The GDG discussed this issue during the development of the guideline and following the submission of comments. The GDG consider that placebo control is inappropriate and unethical when the clinically relevant question is not whether revascularization is better than nothing but whether it is better than standard treatment. To this end there have been multiple studies of PCI vs medical treatment in patients with angina which have confirmed the additional benefit of PCI for symptom relief. These trials have informed the guideline. While placebo control is a practical and readily applicable methodology in the evaluation of new drugs, it is more difficult to apply in the evaluation of procedures. The GDG could not envisage what the placebo arm of a PCI trial would look like or whether "placebo" instrumentation of the coronary circulation would be ethically acceptable. The ethical argument centres around the excess procedural risk that patients in the placebo arm (potentially involving the insertion of catheters across tight coronary stenoses without balloon inflation or stent insertion) would be

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							exposed to compared with those who received active treatment. Similarly it would be practically very difficult to conduct an unbiased sham-controlled study of a procedure that is carried out in fully conscious patients and it is unlikely that such a trial will ever be conducted. *REF: Ezekiel EJ, Miller FG. The ethics of placebo-controlled trials – a middle ground. NEJM 2001;345:915-9.*
SH	National Refractory Angina Centre	5	Full	47	13	**Research recommendations and NICE's reputation** Dimond and Cobb separately showed the potency of the placebo effect in alleviating angina in the pre revascularisation era. Ignoring the laser "revascularisation" trials (see below), no subsequent study has examined the placebo effect in palliative revascularisation. It is illogical and inconsistent of the GDG to make no recommendation regarding the desirability of conducting a trial to exclude the theoretical possibility that PCI is no more effective than a sham procedure. The case for a sham trial of palliative PCI is overwhelming when considering the importance to individual patients and the patient population, national priorities,	Thank you for your comment. The GDG discussed this issue during the development of the guideline and following the submission of comments. The GDG consider that placebo control is inappropriate and unethical when the clinically relevant question is not whether revascularization is better than nothing but whether it is better than standard treatment. To this end there have been multiple studies of PCI vs medical treatment in patients with angina which have confirmed the additional benefit of PCI for symptom relief. These trials have informed the guideline. While placebo control is a practical and readily applicable methodology in the evaluation of new drugs, it is more difficult to apply in the evaluation of procedures. The GDG

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						potential impact on the NHS and future NICE guidance. Such a study would be technically feasible. While there may be ethical concerns about such a trial these matters should be discussed openly and objectively. Arguments that a sham study would be unethical led many patients to undergo transmyocardial laser before claims for its effectiveness were finally discredited. It is important to remember that patients randomised to receive active PCI would be exposed to risk whereas patients randomised to receive sham would be exposed to minimal risk.	could not envisage what the placebo arm of a PCI trial would look like or whether "placebo" instrumentation of the coronary circulation would be ethically acceptable. The ethical argument centres around the excess procedural risk that patients in the placebo arm (potentially involving the insertion of catheters across tight coronary stenoses without balloon inflation or stent insertion) would be exposed to compared with those who received active treatment. Similarly it would be practically very difficult to conduct an unbiased sham-controlled study of a procedure that is carried out in fully conscious patients and it is unlikely that such a trial will ever be conducted. *REF: Ezekiel EJ, Miller FG. The ethics of placebo-controlled trials – a middle ground. NEJM 2001;345:915-9.*
SH	National Refractory Angina Centre	6	Full	399	56	**Patient centred care in refractory angina** Patient centred care is essential for the patient empowerment (self management) approach recommended for "refractory angina" patients. The importance of providing patient centred (or person centred) care to refractory angina sufferers should be acknowledged.	Thank you for your comment. We agree on the importance of patient-centred care for all patients.

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PR	NETSCC Referee 1	1	Full	29	12	**1.1 Are there any important ways in which the work has not fulfilled the declared intentions of the NICE guideline (compared to its scope – attached)** Currently reads **"The following subgroups, were included**" This should read **The following subgroups, who are at special risk, were included**"	Thank you for your comment. These groups are included because they made need special consideration in terms of management, not necessarily because they are at special risk.
PR	NETSCC Referee 1	2	Full	29	28-29	Patients who develop chest pain when anaemic often have underlying angina	Thank you for your comment. This area is covered in another guideline 'Chest pain of recent onset' NICE Clinical Guideline95
PR	NETSCC Referee 1	3	Full	35	2	ACE inhibitors are not a class of drug used for angina. I suggest separating this section into a) drugs used for symptom relief and b) drugs used for prognosis/prophylaxis which more accurately reflects the literature search that follows.	Thank you for your comment. We have introduced additional headings to this list.
PR	NETSCC Referee 1	4	Full	48	1-3	AND	Thank you for your comment. We consider the sentence is correct.
PR	NETSCC Referee 1	5	Full	49	1	It would make more sense to have CG 95 depicted in the diagram to make the investigation and management of stable angina self-contained. At present, it looks like every patient must be tried on three classes of drugs and only then is	Thank you for your comment. We will work with the NICE editors to more clearly indicate the overlap between this guideline and CG95. We have also changed wording of recommendations to indicate when investigations should be

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						intervention offered. Some patients with severe symptoms may warrant a more aggressive approach. Also, it is not clear where investigations should be considered	considered (i.e. newly numbered **recommendation 1.5.1**).
PR	NETSCC Referee 1	6	Full	52	19-21	Not clear If this is the role of the GP or the cardiologist	Thank you for your comment. The wording of this recommendation has been changed following stakeholder consultation.
PR	NETSCC Referee 1	7	Full	52	32	This seems to clash with page 53 line 1-3	Thank you for your comment. The wording of these recommendations has changed following stakeholder consultation.
PR	NETSCC Referee 1	8	Full	44	1-8	Usually, the area of each square is proportional to the study's weight in the meta-analysis. In addition, any confidence interval that crosses the line of unity means that any effect, whether harmful or beneficial, is uncertain.	For guidelines we are interested in whether the effect is clinically important either benefit or harm in order to make recommendations, and this clinically important difference is MID. If the confidence interval crosses the MID, then we are uncertain whether there is a clinically important benefit or no clinically important benefit. However, if the confidence interval does not cross either MID and the whole confidence interval is consistent with no clinically important difference then we have confidence in that finding. Also please note that this figure is not representing a meta-analysis, so the size of the blob is not technically important and it is only schematic.

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PR	NETSCC Referee 1	9	Full	gen		**3.1 How far are the recommendations based on the findings? Are they a) justified i.e. not overstated or understated given the evidence? b) Complete? i.e. are all the important aspects of the evidence reflected?** Comprehensive approach. Findings succinctly summarises the evidence	Thank you for your comment.
PR	NETSCC Referee 1	10	Full	gen		**4.1 Is the whole report readable and well presented? Please comment on the overall style and whether, for example, it is easy to understand how the recommendations have been reached from the evidence.** The document is far too long at over 450 pages. Generally, the shorter the guidance the more likely it is to be read and followed.	Thank you for your comment. The recommendations are summarised in the NICE version and NICE will also develop a Quick Reference Guide for healthcare professionals.
PR	NETSCC Referee 1	11	Full	gen		**4.2 Please comment on whether the research recommendations, if included, are clear and justified.** It is difficult to ascertain the recommendations from the amount of text and supporting literature	Thank you for your comment. The research recommendations are in the format required by NICE.
PR	NETSCC Referee 1	12	Full	55	26	It would be more appropriate to use a named drug such as nifedipine rather than the term dihydropyridine CCB. I would uess that many GPs would not be too sure about which CCB this refers to	Thank you for your comment. We have made this change.
PR	NETSCC Referee 1	13	Full	56	24	Should state when to investigate, not refer to another lengthy document	Thank you for your comment. This recommendation has now been removed from the guideline. The diagnosis of angina is covered by another NICE

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							guideline to which we have to refer. We will work with the NICE editors to ensure that relevant information from the guideline on diagnosis is appropriately referred to in the Quick Reference Guide.
PR	NETSCC Referee 1	14	Full	58	9	Rather than a negative comment, it would make sense to state the positive- when these intervention s should be offered	Thank you for your comment. The GDG did not believe that these interventions have any place in the management of stable angina and wished to make a clear recommendation that they should not be used in the management if stable angina.
PR	NETSCC Referee 1	15	Full	58	14/15	Pain that has not responded to treatment- do the authors here mean that is not angina?	Thank you for your comment. We mean patients whose stable angina has not responded to available and appropriate treatments.
PR	NETSCC Referee 1	16	Full	59	1-7	Some of these may have small vessel disease- to simply tell a patient that he/she has a syndrome is very unsatisfactory and may direct patients to a website for information. When should investigations for small vessel disease be offered?	Thank you for your comment. Recommendations are directed to healthcare professionals. Syndrome X is a diagnosis of exclusion and the GDG considered that further investigation should be considered only on an individual basis.
PR	NETSCC Referee 1	17	Full	gen		The management of stable angina will be influenced by a multitude of factors, not least co-morbidity. This is especially so with respect to intervention.	Thank you for your comment.
PR	NETSCC Referee 1	18	Full	gen		The research base used for this report does not include such complex patients.	Thank you for your comment. The remit for the guideline is Stable Angina and we have included trials for populations. with Stable Angina. Co-morbidities have not been ruled out but we accept that trials

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							can be selective and we have discussed this in the Full guideline.
PR	NETSCC Referee 1	19	Full	gen		As a result, I believe that, despite the best intentions of the NICE team, this report will impact very little on the way patients with stable angina will be managed in general practice and in cardiology practice.	Thank you for your comment.
PR	NETSCC Referee 1	20	Full	gen		The fact that there are so many drug trials and intervention trials is more commercially driven than to add to the research base and so many add even less value to this analysis.	Thank you for your comment.
PR	NETSCC Referee 1	21	Full	gen		I believe that the economic analysis will be of even less help to practicing clinicians.	Thank you for your comment. Health economics is part of NICE Guidelines because we aim to achieve efficiency in the use of the NHS budget. The final aim of economic analyses is to identify strategies to obtain better health outcomes from available resources.
PR	NETSCC Referee 2	1	Full	General		**1.1 Are there any important ways in which the work has not fulfilled the declared intentions of the NICE guideline (compared to its scope – attached)** Scope - I may have missed or not seen in the document with the sub-headings relating to discussion about: people south Asian origin, people older than 85 years and women.	Thank you for your comment. The recommendations and evidence to recommendations for these groups is in **section 11.7**. Comment on the lack of evidence is also included in individual evidence to recommendations sections of the guideline.
PR	NETSCC Referee 2	2	Full	General		**2.1 Please comment on the validity of the work i.e. the quality of the methods and**	Thank you for your comment.

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						their application (the methods should comply with NICE's Guidelines Manual available at http://www.nice.org.uk/page.aspx?o=guidelinesmanual). It gives me a great pleasure to congratulate the GDG members and the NICE guideline staff that they have worked very hard to put together a well-organized and an easy to read a piece of work. Well done!! The GDG have employed appropriate quality outcome measures to judge the available literature consistently throughout the document. In my view the review, comply with the NICE Guidelines manual.	
PR	NETSCC Referee 2	3	Full	356	16:3	**2.2 Please comment on the health economics and/or statistical issues depending on your area of expertise.** General - The economic conclusion and clinical outcome conclusions need to be linked more closely and in line with the recommendation.	Thank you for your comment. We have edited the economic considerations, quality of evidence and other considerations sessions in the evidence to recommendation section to clarify the link between the economic evidence, clinical outcome conclusions and the recommendation.
PR	NETSCC Referee 2	4	Full	326		**3.1 How far are the recommendations based on the findings? Are they a) justified i.e. not overstated or understated given the evidence? b) Complete? i.e. are all the important aspects of the evidence reflected?** General - It would be useful to make a comment on the composition of	Thank you for your comment. We are not recommending comprehensive cardiac rehabilitation programmes.

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						multidisciplinary care team and the requirements of the core team to run cardiac rehabilitation programme. In addition, briefly comment on the duration of comprehensive cardiac rehabilitation and maintenance programme.	
PR	NETSCC Referee 2	5	Full	336		**3.2 Are any important limitations of the evidence clearly described and discussed?**	Thank you for your comment. We have amended the section including the limitations of the study.
PR	NETSCC Referee 2	6	Full	General		In places because of the scarcity of the literature some articles have been reviewed which are not satisfying the review criteria. This should be acknowledged in the text in the recommendation section.	Thank you for your comment. We have worded the recommendations according to the confidence of the GDG in quality of evidence for the outcomes. It is not customary to include comment on the evidence in the recommendation section.
PR	NETSCC Referee 2	7	Full	General		**4.1 Is the whole report readable and well presented? Please comment on the overall style and whether, for example, it is easy to understand how the recommendations have been reached from the evidence.** In my areas of expertise on rehabilitation most of the recommendations were drawn from the available evidence by appraising the literature	Thank you for your comment
PR	NETSCC Referee 2	8	Full	326		General - Are there any studies that examined the benefits of cardiac rehabilitation on morbidity, mortality and healthcare utilization for patients with stable angina? If so, it would be useful to include in order to enhance the importance of cardiac	Thank you for your comment. These outcomes were included in our protocol when searching for evidence on cardiac rehabilitation. We did not find evidence using these outcomes.

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						rehabilitation and evidence for healthcare providers.	
PR	NETSCC Referee 2	9	Full	405		**4.2 Please comment on whether the research recommendations, if included, are clear and justified.** General -It would be useful to comment for a keen reader in the clinical section the importance of specific attention to the role of psychological factors in pain and development of skills to modify cognitions' and behaviours associated with pain.	Thank you for your comment. The page number refers to the recommendations and link to evidence for self-management programmes. Attention to the role of psychological factors and the development of skills are both included in the recommendation. It is beyond the scope of a guideline to more generally discuss psychological factors in pain and the development of skills to modify cognitions and behaviours associated with pain.
PR	NETSCC Referee 2	10	Full	363	3-5	I wonder whether this might help. "Is an 8-week, comprehensive, multidisciplinary, cardiac rehabilitation service whether improves mortality and cost effective for managing stable angina than the usual care"?	Thank you for your comment. The current wording was agreed with the NICE editor.
PR	NETSCC Referee 2	11	Full	328-433		All tables - All the tables should be checked for the quality rating that signify with low should be with two (++) rather than with three (+++).	Thank you for your comments. We have amended the table accordingly.
PR	NETSCC Referee 2	12	Full	371		No page - Aucamp (1992) study – How long was the follow-up?	Thank you for your comment. The follow-up was at the end of the trial.
PR	NETSCC Referee 2	13	Full	336	5-9	It would be helpful for the additional data to be more informative e.g. duration of intervention, follow-up, mean age and relevant outcomes etc.	Thank you for your comment. Additional details of the population, intervention, outcomes and follow-up of the studies are reported in the respective evidence tables (see appendix) .

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PR	NETSCC Referee 2	14	Full	346	3-4	It might be better to say "There was significantly more frequent cardiac rehospitalisation in the control group'...	Thank you for your comment. We have amended the relevant sentence accordingly.
PR	NETSCC Referee 2	15	Full	347		General - What was the primary outcome for the study? Have the authors reported the findings using the 95% confidence interval?	Thank you for your comment. The primary outcome in the study was health behaviours (walking performance, step II diet adherence and medication adherence, smoking cessation). The authors have reported mean and SD.
PR	NETSCC Referee 2	16	Full	348	11	- "Exercise – consisted of 10 simple aerobic exercises designed to improve..."	Thank you for your comment. The wording has been taken directly from the paper.
PR	NETSCC Referee 2	17	Full	348	12	- Psychological status more comment is needed. E.g. using CBT principle etc	Thank you for your comment. Details of the intervention are in the evidence tables in the appendix.
PR	NETSCC Referee 2	18	Full	349	3	'blinded to occasion' is not clear. Please explain.	Thank you for your comment. The wording 'Occasion' has been taken directly from the paper. The word 'Occasion' has been used to refer to the follow-ups in the trial and we understand this to be related to time point of follow up..
PR	NETSCC Referee 2	19	Full	354	15	It reads better to say – "a score > 11 indicates a potential "case" for clinical anxiety or depression".	Thank you for your comment. We have amended the relevant sentence accordingly
PR	NETSCC Referee 2	20	Full	356		Todd (1990) ...follow up were not 'statistically' significant... Hambrercht (2004) ..... cerebrovascular accidents ... delete the extra bracket.	Thank you for your comment. We have amended the relevant evidence statements accordingly.
PR	NETSCC	21	Full	357 -		Bundy (1994, 1998) – Stress management	Thank you for your comments. We have

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	Referee 2			358		vs routine care control. I could not find to read the article. I wonder that the intervention period was 8 weeks – rather than the follow up period after the intervention. It requires checking.	checked the original article, the follow-up for this study was: 1) at immediately after the 8 week intervention and 2) at 8 weeks after the intervention.
PR	NETSCC Referee 2	22	Full	358		Ornish (1998) – Evidence from one RCT shows that there "was" no "statistically" significant difference...	Thank you for your comment. We have amended the relevant evidence statement accordingly.
PR	NETSCC Referee 2	23	Full	359		Jiang 2007 ... significantly higher in the Nurse "led" cardiac rehabilitation programme. It would be helpful to state the p-value.	Thank you for your comment. We do not include the p-values in the evidence statement. Only MD or RR with their respective CIs are stated in the evidence statements.
PR	NETSCC Referee 2	24	Full	360	16.5	SEI QOL-DW - please state in full.	Thank you for your comment. We have amended the relevant paragraph accordingly.
PR	NETSCC Referee 2	25	Full	360		Dealing with stress, 'anxiety' or depression	Thank you for your comment. We have rechecked the evidence review and added anxiety to the recommendation.
PR	NETSCC Referee 2	26	Full	361		Under quality of evidence second paragraph on 8th line - The study had a very small 'sample' size (n = 42)...	Thank you for your comment. We have amended the relevant paragraph accordingly.
PR	NETSCC Referee 2	27	Full	359		Jiang 2007 ... significantly higher in the Nurse "led" cardiac rehabilitation programme. It would be helpful to state the p-value.	Thank you for your comment. We do not include the p-values in the evidence statement. Only MD or RR with their respective CIs are stated in the evidence statements.
PR	NETSCC Referee 2	28	Full	360		SEI QOL-DW - please state in full.	Thank you for your comment. We have amended the relevant paragraph accordingly.

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PR	NETSCC Referee 2	29	Full		16.5	Dealing with stress, 'anxiety' or depression	Thank you for your comment. We have rechecked the evidence review and added anxiety to the recommendation.
PR	NETSCC Referee 2	30	Full	361		Under quality of evidence second paragraph on 8th line - The study had a very small 'sample' size (n = 42)...	Thank you for your comment. We have amended the relevant paragraph accordingly.
PR	NETSCC Referee 2	31	Full	375	16-17	Side effects – second sentence – It reads better, "Headache and constipation were reported by two patients who were on placebo group".	Thank you for your comment. We have amended the relevant sentence accordingly.
PR	NETSCC Referee 2	32	Full	376-377		Other consideration – Last sentence is very long and lacks clarity. Please re-write.	Thank you for your comment. We have re-written this sentence.
PR	NETSCC Referee 2	33	Full	390	6	What is the mean age of the patients compared with the whole study population? Women were not included in the study.	Thank you for your comment. We have added more detail about gender and age of whole study and subgroup population. There were 18 women in the whole study (study population 137).
PR	NETSCC Referee 2	34	Full	General	7,29	Health related quality of life (HRQOL), HRQOL	Thank you for your comments. We have amended the relevant sections accordingly.
PR	NETSCC Referee 2	35	Full	398		Ritcher 1991 - How long was the follow-up period?	Thank you for your comment. The follow-up was immediately after 4 week treatment period. This is described in the table at the start of the section but we have now also added this information to the evidence statement.
PR	NETSCC Referee 2	36	Full	404		Please check the correct article whether it was reviewed the Payne 1994 or Payne	Thank you for your comment. The reviewed paper was Payne 1994.

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						2004 (reference 219).	
PR	NETSCC Referee 2	37	Full	419		The majority of the evidence is low quality. It is not moderate quality.	Thank you for your comment. We have amended the relevant paragraph accordingly.
SH	NHS Direct	1	Full	gen		NHS Direct have no comments on the content of the draft guideline and welcome its publication.	Thank you for your comment.
SH	Pfizer Ltd	1	Full	General		We welcome this guideline concerning the management of stable angina.	Thank you for your comment.
SH	Pfizer Ltd	2	Nice	11	1.2.8	We welcome this reference to CG67: "Offer statin treatment in line with 'Lipid modification' (NICE clinical guideline 67)."	Thank you for your comment.
SH	PRIMARY CARE CARDIOVASCULAR SOCIETY	1	Full	GENERAL	GENERAL	**NICE GUIDELINE ON STABLE ANGINA** The Primary Care Cardiovascular Society welcomes the recent draft NICE Guideline on Stable Angina, which provides a concise and practical approach to the management of the increasing number of patients in the community with established coronary heart disease. This Guidance will assist clinicians improve not only their patients' symptom control, and hence quality of life, but also their long-term prognosis. In terms of the assessment, and risk stratification, of those individuals with stable angina, it would be helpful for the	Thank you for your comment and references. The management of modifiable risk factors was outside the scope of this guideline. The GDG recognised the important of these aspects of management and have made reference to other guidance where available. We will work with the NICE editors when preparing the Quick Reference guide to ensure these areas are adequately signposted. The GDG discussed the role of heart rate in the treatment of angina and were aware of evidence linking heart rate to ischaemia and outcomes. The GDG did not chose heart rate as an

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						Guidelines to acknowledge the importance of active management of modifiable risk factors, including BP, heart rate, dyslipidaemia, excessive weight, smoking and alcohol intake. There is a substantial body of evidence to support the optimal management of co-existing hypertension and this is also supported by significant data demonstrating the improvement in symptom control, and outcomes, in controlling heart rate in individuals with coronary heart disease. (1) Heart rate has a significant impact in determining both coronary perfusion and myocardial oxygen demand. Intervening to optimize heart rate control, whether through lifestyle interventions or pharmacotherapy, has a positive effect on the ischaemic burden and, as a result, patient symptoms and prognosis. As such, a strategy to ensure good heart rate control should be an essential part of any approach to optimize medical therapy in angina patients. A considerable evidence base shows that an elevated resting heart rate is associated with a significantly increased risk of cardiovascular events. (2)	outcome when assessing interventions for angina as heart rate was considered a surrogate endpoint . The major outcomes chosen by the GDG were angina symptoms as well as measures of angina related morbidity and mortality. The GDG considered that treating to a symptomatic end point of angina symptoms was more appropriate than treating to a specific heart rate. We have reviewed the guidelines mentioned to ensure we have not missed any evidence. The current SIGN guideline discussed heart rate in relation to full beta blockade but does not recommend treating to a specified heart rate. The European Society of Cardiology does not recommend treating to a specific rate. The AHA guideline says it is customary to treat to a specific heart rate but does not provide evidence of an effect on major outcomes.

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						In addition heart rate is an important risk marker that can be very simply measured in a clinical setting. This NICE Guideline would be an ideal opportunity to highlight the importance of this, as part of a patient's overall clinical assessment, to help identify those with underlying residual risk, as well as potentially identifying other significant conditions, e.g. atrial fibrillation. Several international Guidelines, including SIGN (3), the European Society of Cardiology (4) and American Heart Association (5) endorse the principle of treating to a specified heart rate in patients with stable angina, recognizing the importance in this high-risk group, of ensuring optimal heart rate control. With this evidence it would be an ideal opportunity for the Guideline Development Group to emphasize the importance a comprehensive clinical assessment, including blood pressure, heart rate and dyslipidaemia, and actively managing these modifiable risk factors to improve patient symptom control, quality of life and outcomes. **References:** (1) Lang CC, Gupta D, Kalra P et al.	

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						Elevated heart rate and cardiovascular outcomes in patients with coronary artery disease: clinical evidence and pathophysiological mechanisms. Atherosclerosis (2010), doi:10.1016/j.atherosclerosis.2010.01.029 (2) Kollach R et al. Eur Heart J. 2008;29:1327-1334 (3) Scottish Intercollegiate Guidelines Network. Management of stable angina. Edinburgh: NHS Quality Improvement Scotland; 2007. Report No: 96 (4) Fox et al. Guidelines on the Management of Stable Angina. Eur Heart J. 2006;27:1341-1381 (5) Gibbons RJ, et al. ACC/AHA Practice Guidelines 2002. 1-124	
SH	RCGP	1	Nice	6		The guideline makes reference to patient centred care which is welcomed and embraced by the RCGP. The concept of shared decision making is to be encouraged and the RCGP have an interest in promoting this	Thank you for your comment.
SH	RCGP	2	Nice	7		The key priorities for implementation are logical and clear. Many are obviously relevant for cardiology assessment. However the approach taken of recommending multidisciplinary input is	Thank you for your comment.

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						welcome	
SH	RCGP	3	Nice	8		The recommendation of 1.4.11 is important and is relevant to patients and GPs	Thank you for your comment.
SH	RCGP	4	Nice	9		The information provided from 1.1.1 to 1.1.7 is clear. Making explicit the advice about addressing sexual activity is important	Thank you for your comment.
SH	RCGP	5	Nice	10		The advice about treating episodes of angina is very important and clearly written	Thank you for your comment.
SH	RCGP	6	Nice	11		My experience has been that fish oils have been recommended by specialists.	Thank you for your comment. The evidence does not support their use in patients with Stable Angina.
SH	RCGP	7	Nice	12		Not familiar with ranolazine	Thank you for your comment. Ranolazine is licensed as adjunctive therapy in patients with stable angina who are inadequately controlled or intolerant of first-line anti-anginal drugs.
SH	RCGP	8	Nice	14-16		Clear but aimed at the specialist	Thank you for your comment.
SH	RCGP	9	Nice	General		The sections aimed at General Practice are clear and not controversial as standard clinical practice	Thank you for your comment.
SH	Royal College of Nursing	1	Full	General		The Royal College of Nursing welcomes this guideline. It is comprehensive and timely.	Thank you for your comment.
SH	Royal College of Nursing	2	Nice	6		Patient-centred care: We agree that good communication between the healthcare professional and the patient is essential and we welcome proposals to tailor written evidenced-based patient information which would inform patients about the treatment and care they are given. This is in line with Principle D of	Thank you for your comment.

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						the Principles of Nursing Practice (RCN 2010) which tells us what patients, families and carers expect from nursing. Nurses and nursing staff provide and promote care that puts people at the centre, i.e. by involving patients, service users, their families and carers in decisions and helping them make informed choices about their treatment. (www.rcn.org.uk/nursingprinciples)	
SH	Royal College of Pathologists	1	Full	gen	gen	the Royal College of Pathologists has no comments to make at this stage of the development process	Thank you for your comment.
SH	Servier Laboratories	1	Full	55	26	The **footnote (3)** stating: *"Ivabradine should only be combined with a dihydropyridine calcium channel blocker",* may lead to misunderstandings as it could be misread as suggesting ivabradine can only be combined with a calcium channel blocker. Servier would therefore like to suggest an alteration to ensure clarity of meaning: *"when ivabradine is combined with a calcium channel blocker, a dihydropyridine calcium channel blocker should be used."*	Thank you for your comment. We have made this change to the footnote.
SH	Servier Laboratories	2	Full	128,129		**Please note that the following comments relate to page 128, paragraph 6 and page 129, paragraph 2:** Ivabradine has one of the largest and most comprehensive safety datasets amongst all	Thank you for your comment. The remit of this guideline is stable angina and the statements made refer to the use of ivabradine in stable angina. We have added to these sentences to make this clear. While the evidence for safety does

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						available anti-anginal therapies, from both patient case reports and clinical trials, dating from at least 2005. Servier would therefore ask the GDG to take into account the following information and to subsequently consider revision of the statements: **Page 128, paragraph 6:** *"Evidence confirming the long term efficacy and safety of ivabradine is limited"* **Page 129, paragraph 2:** *"Ivabradine is a relatively new drug with limited information about long term safety and efficacy"* Ivabradine was first launched in the UK in December 2005 and has thus been available for use by health care professionals here for over 5 years. In addition, over 10,000 patients have now been studied to date in phase II and III trials[1-7]. During these trials, no emergent safety signals were observed and the most frequently reported events were already known and/or pharmacologically predictable and reversible. For example: • Sinus bradycardia has been reported in 3.3% of patients in monotherapy, with	not come from studies of patients with stable angina, we accept that there is evidence in other areas and have removed this part of the sentence. We have looked at outcomes demonstrating symptom relief (i.e. free of angina/frequency of angina) and long term outcomes such as mortality, MI. The GDG considered that improvement in heart rate is a surrogate outcome…

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						0.5% of patients experiencing a severe bradycardia below or equal to 40 bpm. In the ASSOCIATE study, 1.1% of patients experienced symptomatic bradycardia in combination with beta-blockers[6,8] • Fewer than 1% of patients are thought to change their daily routine or discontinue treatment due to visual effects[8] Of particular note, two large outcome trials in high risk, advanced cardiovascular disease populations also provide indications of product safety: A large outcome study, BEAUTIFUL[5], was performed in 10,917 patients with coronary artery disease and left ventricular dysfunction (LVEF <40%) on top of optimal background therapy (86.9% of patients were receiving beta-blockers). Over a median duration of follow-up of 19 months, no difference was seen in serious AEs, including cardiac disorders, between the ivabradine and placebo groups. A recently published pre-planned substudy of the BEAUTIFUL trial[9] explored the cardiac safety of ivabradine in 840 patients with stable coronary artery disease and left ventricular dysfunction (LVD) and who were receiving optimal background therapy,	

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						(ivabradine 5 or 7.5 mg/day, n = 421; placebo, n = 419). 93% of these patients were also taking beta-blockers. Ambulatory 24-hour electrocardiographic Holter monitoring was performed at baseline and after 1 month and 6 months**.** Observations regarding incidence of bradycardia, in this study, were in line with the safety assessment of the main study. Furthermore, there was no increase in incidence of conduction and rhythm disturbances. While the BEAUTIFUL study was a study of patients with coronary artery disease and left ventricular dysfunction, rather than stable angina, it included enough stable angina patients to make both a meaningful analysis of safety in this at risk LVD population, and an exploratory analysis of efficacy: In a post-hoc analysis[10] of a subgroup of patients, with symptomatic angina at randomisation (n=1507), no safety signal was identified regarding cardiovascular death, hospitalisation for acute MI or heart failure (ivabradine 12.0% vs. placebo 15.5%, p=0.05). In 2010, a study of over 6500 patients with chronic heart failure, on guidelines-based treatment, comparing morbidity and mortality outcomes in patients taking ivabradine *vs* placebo, also demonstrated the tolerability of ivabradine[7]. Heart failure	

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						was of ischaemic cause in 68% of patients and 89% patients were also taking a beta-blocker. Of note, the total number of AEs was lower in the ivabradine group than in the placebo group (p=0·025). Bradycardia requiring withdrawal was 1% in the ivabradine group, compared to the placebo group. In addition, fewer than 1% of patients in both groups withdrew due to phosphenes. **References:** 1. Borer JS, Fox K, Jaillon P et al. Antianginal and antiischemic effects of ivabradine, an I(f) inhibitor, in stable angina: A randomized, double-blind, multicentered, placebo-controlled trial. *Circulation* 2003;107:817-23 2. Tardif JC, Ford I, Tendera M et al. Efficacy of ivabradine, a new selective I(f) inhibitor, compared with atenolol in patients with chronic stable angina. *Eur Heart J* 2005; 26:2529-36 3. Ruzyllo W, Tendera M, Ford I et al. Antianginal efficacy and safety of ivabradine compared with amlodipine in patients with stable effort angina pectoris: A 3-month randomised, double-blind, multicentre, noninferiority trial. *Drugs* 2007; 67:393-405 4. Lopez-Bescos L, Filipova S, Martos R et al et al. Long-Term Safety and Efficacy	

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						of Ivabradine in Patients with Chronic Stable Angina Cardiology 2007; 108:387–396 5. Fox KM, Ford I, Steg PG et al. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. Lancet 2008; 372:807-16 6. Tardif JC, Ponikowski P, Kahan T et al. Efficacy of the I(f) current inhibitor ivabradine in patients with chronic stable angina receiving beta-blocker therapy: a 4-month, randomized, placebo-controlled trial. *Eur Heart J* 2009; 30:540-8 7. Swedberg K, Komajda M, Böhm M et al. on behalf of the SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet 2010; 376:875-85 8. Procoralan▼ Summary of Product Characteristics. Available from URL: http://www.medicines.org.uk/EMC/medicine/17188/SPC/Procoralan/ Accessed on 31/1/11 9. Tendera M, Talajic M, Robertson M et al. Safety of Ivabradine in Patients With Coronary Artery Disease and Left	

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						Ventricular Systolic Dysfunction (from the BEAUTIFUL Holter Substudy). Am J Cardiol 2011 10. Fox KM, Ford I, Steg PG et al. Relationship between ivabradine treatment and cardiovascular outcomes in patients with stable coronary artery disease and left ventricular systolic dysfunction with limiting angina: a subgroup analysis of the randomized controlled BEAUTIFUL trial. *Eur Heart J* 2009; 30:2337-45	
SH	Servier Laboratories	3	Full	128		**Please note that the following comments relate to page 128, paragraph 3:** It is stated on page 128: *"In addition there is a statistically significant incremental benefit of adding ivabradine to atenolol in people with angina, but the magnitude of the benefit is small and of uncertain clinical significance".* Servier would like to propose that the last part of this statement is removed in order to reflect the evidence shown here regarding the clinical significance of combining ivabradine with beta-blockers.	Thank you for your comment. We have altered the sentence following your comment to clarify the intent of the GDG. We agree that there is a statistically significant incremental benefit of adding ivabradine to atenolol in terms of total exercise duration. The GDG noted that although the mean difference between groups at 4 months was 16 secs, the CI was from 8secs to 25secs. The GDG acknowledge that this benefit does compare well with older drugs however the GDG do consider that at the lower CI clinical significance for patients is highly uncertain.

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						In the ASSOCIATE study[1], a sixteen second improvement of total exercise duration was seen at stage three of the BRUCE protocol where the functional capacity of an individual is approximately 9 METs, corresponding to activities considered to be of high intensity i.e. bicycling at ~25km/h, jogging at ~9km/h, cross-country skiing at ~8km/h. We would also like to highlight the acknowledgement by the GDG that evidence for combination therapy with a BB and a CCB compared to BB or CCB alone is weak and, that evidence to support the addition of long-acting nitrate to monotherapy with BB or CCB in people with stable angina is very weak. In the interest of transparency, fairness and balance, we would therefore like to draw the attention of the GDG to the strength of data available for the combination of newer anti-anginal agents[1-3], compared with traditional treatment options. The relevance of the statistically significant positive results of the ASSOCIATE study[1] is evident when one considers that: **The 16s improvement in TED observed during the third stage of the Bruce**	There is no evidence of effect longer term morbidity and mortality outcomes for use of ivabradine in patients with stable angina. We have included in the evidence review the 3 trials in the submitted reference list ASSOCIATE study, BEAUTIFUL study and the ERICA trial. The other references submitted are not included in the guideline because (1) the population is not people with stable angina (SHIFT study) or (2) the outcomes reported by the studies were not outcomes chosen by the GDG to inform recommendations.

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						protocol was observed during a period of high metabolic energy expenditure and at trough of drug effect. • The primary efficacy criterion was total exercise duration (TED) of an exercise tolerance test (ETT), in accordance with EU guidelines[4]. As patients received usual background therapy, as determined by their treating clinician (atenolol 50 mg o.d.), the standard Bruce exercise protocol was chosen. The improvement in TED in ASSOCIATE of 16 s ($p < 0.001$) was achieved, most commonly, during the third stage of the standard Bruce protocol, which represents a substantial workload (treadmill speed 5.5 km/h, gradient 14%) Such changes can be expected to have a great impact on patients' daily activities. The improvement in TED was accompanied by improvements in time to angina onset (TAO) of 25 s ($p < 0.001$) and in time to 1 mm ST segment depression (TST) of 28 s ($p < 0.001$). • In stage 3 of the Bruce protocol, where most patients in ASSOCIATE had their improvement in TED, the functional capacity of an individual is approximately 9 METs, corresponding to activities considered to be of high	

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						intensity i.e. bicycling at ~25km/h, jogging at ~9km/h, cross-country skiing at ~8km/h[5]. The translation of total exercise capacity into Metabolic Equivalents (METs)* can provide a standard measure of performance[5]. **Based on literature reviews these data represent a rare and compelling demonstration of the benefit of combining two anti-anginal drugs.** • Most published studies of combination anti-anginal therapy have shown only small and statistically non-significant benefits of the combination on ETT criteria at the trough of drug activity. In the meta-analysis of well-recognised and accepted combinations of anti-anginal treatments performed by Klein[6] *et al*, the difference in TED, observed at trough of drug activity, between the combination of calcium antagonists and beta-blockers and beta-blockers as monotherapy was only 4s and was not statistically significant. • In the ASSOCIATE study the improvement in TED was in accordance with the improvements observed in time to limiting angina (TLA), time to angina onset (TAO) and time to 1 mm ST segment depression (TST). The mean improvements in TAO	

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						and in TST (which is an objective criterion of ischaemia), were 25 s ($p < 0.001$) and 28 s ($p < 0.001$) respectively. These improvements are all statistically significant and cannot be regarded as minimal when considering the workload at this stage of the exercise. • In the ivabradine group 70% of patients improved their TED and 49% of patients improved their TED by more than 30s. **Sub-group analyses show ivabradine to have anti-anginal efficacy in both patients who are maximally beta-blocked, and also in patients who have a HR of <65bpm.** • A sub-analysis of the ASSOCIATE study demonstrated that, in patients with a relatively low HR (≤ 65 bpm) at baseline (n=224), ivabradine retained its efficacy[7]. Similar efficacy was also demonstrated in a second analysis[8] in a population (n=144) that could be considered optimally treated with beta-blocker, either because of a resting HR < 60 bpm, SBP < 100 mm Hg or PR > 200 ms. Finally, with regards to safety and tolerability, the combination of ivabradine	

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						with beta-blocker has been assessed in a number of studies across cardiovascular indications, including ASSOCIATE[1] (n=889), BEAUTIFUL[9,10] (n=10,917) and the SHIFT[11] (6,505) study. BEAUTIFUL and SHIFT were large, robust RCTs of patients with advanced cardiovascular disease providing data that build upon the already considerable safety dataset in angina. * One MET is defined as the amount of oxygen consumed by an average individual while sitting at rest and is equal to 3.5 ml O_2/kg per minute. The energy cost of an activity can be determined by dividing the relative oxygen cost of the activity (ml O_2/kg/min) by 3.5, and provides a convenient method to describe the functional capacity i.e. exercise tolerance of an individual as determined from progressive exercise testing. **References:** 1. Tardif JC, Ponikowski P, Kahan T et al. Efficacy of the I(f) current inhibitor ivabradine in patients with chronic stable angina receiving beta-blocker therapy: a 4-month, randomized, placebo-controlled trial. *Eur Heart J* 2009; 30:540-8	

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Type	Stakeholder	Order no.	Doc	Page No	Line No	Comments	Developer's response
						2. Chaitman BR, Pepine CJ, Parker JO et al. Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina: a randomized controlled trial. Journal of the American Medical Association 13 2004; 291:309-6 3. Stone PH, Gratsiansky NA, Blokhin A et al. Antianginal efficacy of ranolazine when added to treatment with amlodipine. The ERICA (Efficacy of Ranolazine in Chronic Angina) trial. J Am Coll Cardiol 2006; 48:566-75 4. The Clinical Investigation Of Anti-Anginal Medicinal Products In Stable Angina Pectoris - CPMP/EWP/234/95 rev 1, 2006 5. Jette M, Sidney K, Blumchen G. Metabolic Equivalents (METS) in Exercise Testing, Exercise Prescription, and Evaluation of Functional Capacity. Clin. Cardiol. 1990: 13:*555-565* 6. Klein W, Jackson G, and Tavazzi L. Efficacy of monotherapy compared with combined antianginal drugs in the treatment of chronic stable angina pectoris: a meta-analysis. Coronary Artery Disease 2002: Vol 13 No 8 7. Tardif J, Ponikowski P, Kahan T et al. Ivabradine improves exercise capacity	

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						in patients with stable angina receiving beta-blockers independent of baseline HR: a subgroup analysis of the ASSOCIATE study. Eur Heart J 2010 Vol 31 (Suppl 1) 8. Tardif J, Ponikowski P, Kahan T et al. Ivabradine improves exercise capacity in patients with stable angina pectoris receiving maximal tolerated dose of beta-blockers: a subgroup analysis of the ASSOCIATE study. Eur Heart J 2010 Vol 31 (Suppl 1) 9. Fox KM, Ford I, Steg PG et al. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. Lancet 2008; 372:807-16 10. Fox KM, Ford I, Steg PG et al. Relationship between ivabradine treatment and cardiovascular outcomes in patients with stable coronary artery disease and left ventricular systolic dysfunction with limiting angina: a subgroup analysis of the randomized controlled BEAUTIFUL trial. Eur Heart J 2009; 30:2337-45 11. Swedberg K, Komajda M, Böhm M et al. on behalf of the SHIFT Investigators. Ivabradine and outcomes in chronic	

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						heart failure (SHIFT): a randomised placebo-controlled study Lancet 2010; 376:875-85	
SH	Servier Laboratories	4	Full	55	8 & 11	**Please note that the following comments relate to page 55, line 8, page 55, line 11 and page 56, lines 1, 11 and 19:** Servier would like to highlight the importance of the role of heart rate for the selection and optimisation of appropriate treatment in chronic stable angina patients for the following reasons: • Myocardial ischaemia results from an imbalance between coronary perfusion and myocardial oxygen demand. Heart rate is the major determinant for both myocardial oxygen demand and oxygen supply • Patients with higher heart rates are at greater risk of angina attacks • Measurement of heart rate is a simple guide to beta-blocker response and adherence • International guidelines, including ESC, AHA and SIGN, endorse the importance of heart rate control in the management of angina The choice of an appropriate anti-anginal treatment depends on the heart rate of a patient. For example, the treatment of a	The GDG discussed the role of heart rate in the treatment of angina and were aware evidence linking heart rate to ischaemia and outcomes. The GDG did not chose heart rate as an outcome when assessing interventions for angina as heart rate was considered a surrogate endpoint. The outcomes chosen by the GDG were angina symptoms as well as measures of angina related morbidity and mortality. The GDG considered that treating to a symptomatic end point of angina symptoms was more appropriate than treating to a specific heart rate. We have reviewed the guidelines quoted to ensure we have not missed any evidence. The AHA guideline says it is customary to treat to a specific heart rate but does not provide evidence of an effect on major outcomes. The SIGN guideline discussed heart rate in relation to full beta blockade but does not recommend

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						patient with a heart rate of ≥ 80 beats per minute (bpm) would be quite different to one with a heart rate of <60bpm, the difference being the underlying ischaemic burden of those patients. The intrinsic role of heart rate in the treatment of angina is recognised by the longstanding place of beta-blockers as first line therapy. In addition, when a patient reaches the maximal tolerated dose of an anti-anginal, heart rate is an excellent guide to the next step in therapy. For these reasons, and in relation to the evidence set out below, we would like to propose revisions of the following statements: Where on Page 55, line 8 it is advised: *"Titrate the drug dosage against symptoms up to the maximum tolerable dosage*"; we would like to propose this is changed to: *"Titrate the drug dosage against symptoms up to the maximum tolerable dosage, according to side effects, heart rate and blood pressure".* Where on Page 55, line 11 and page 56, lines 1, 11 and 19 it is stated**: "***Decide which drug to use based on comorbidities, contraindications, the person's preference and costs",* we would like to propose this is	treating to a specified heart rate. The European guideline (ref 4) do not recommend treating to a specific heart rate Clinical trial evidence reviewed for treatment of stable angina does not support a recommendation that all patients with stable angina should be on at least on rate-limiting drug. The treatment of blood pressure is outside the scope of the guideline but we will work with NICE editors to ensure adequate reference to other NICE guidance for hypertension and will ensure this is adequately signposted in the Quick Reference Guide.

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						changed to: "*Decide which drug to use based on comorbidities, clinical markers including heart rate and blood pressure, contraindications, the person's preference and costs".* **Pathophysiology:** The pathophysiological processes underlying the development of myocardial ischaemia (and the therefore the subsequent clinical syndrome of angina) are complex and dynamic[1] but essentially the cause is an imbalance between myocardial coronary blood flow supply and myocardial oxygen consumption. Heart rate has been shown to be an important determinant of both coronary perfusion and myocardial oxygen demand; an increased HR increases cardiac work, as well as shortening the diastolic filling time, which subsequently adversely affects coronary blood flow[2-3]. **Elevated heart rate is linked to ischaemia:** The relationship between elevated heart rate and the incidence of ischaemia in patients with stable angina has been demonstrated in a number of studies. The Angina and Silent Ischaemia study (ASIS)[4] showed that a rise in heart rate of ≥5bpm	

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						preceded over 80% of ischaemic episodes and that the likelihood of developing ischaemia was proportional to the baseline heart rate, as well as both the magnitude and duration of the heart rate increase. In addition, it showed that patients with a resting heart rate of ≥80bpm were twice as likely to experience an ischaemic episode as patients with a resting heart rate of 60 bpm or less. Similarly, in a study looking at a sub group of 235 patients from the Asymptomatic Cardiac Ischaemia Pilot (ACIP)[5], an association between mean heart rate and ischemia on ambulatory electrocardiography after 12 weeks was observed. Patients with a mean heart rate >80 bpm were shown to have a twofold increase in detectable ischaemia compared to those with a mean heart rate <70 bpm. In another study looking to determine the triggers of silent and symptomatic ischaemia in daily life, the heart rate at onset of ischaemia appeared to parallel the symptoms of angina, with symptomatic episodes having a higher heart rate[6]. Kop *et al* also showed that heart rates gradually increased in the 60-min to 20-min interval before the ischemic event (p=0.04) followed by a more pronounced increase in the 4 min before ischemia (p=0.008)[7].	

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						Controlling heart rate fundamentally reduces cardiac ischaemia: Reducing heart rate in angina has favourable effects on the ischaemic burden by increasing diastolic time and thus coronary perfusion, as well as reducing oxygen demand[2]. Adequate control of heart rate is therefore fundamental to optimising medical therapy in patients with angina[8]. Indeed the primary driver for the discovery of beta-blockers was the desire to reduce heart rate in order to manage stable angina: Nobel Prize winner, Sir James Black, discovered the first beta-blocker, propranolol, in his search for a drug treatment to counteract the tachycardia he observed in angina patients[9]. The heart rate lowering actions of both BBs and non-dihydropyridine CCBs for the treatment of stable angina are well established[10]. However, both classes also have multiple, relatively non-specific cardiovascular actions and do not solely reduce heart rate. The data behind ivabradine, a newer class of agent, with pure heart rate lowering properties, have confirmed the critical role of heart rate in the management of stable angina, as witnessed by an RCT showing non-inferiority of ivabradine *vs* beta-blockers, for all exercise tolerance test parameters over 4 months[11].	

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						The addition of ivabradine to a beta-blocker (atenolol) at the commonly used dosage in clinical practice in patients with stable angina produced significant additional efficacy with no untoward effect on safety or tolerability[12]. This was attributable to the additional heart rate reduction in those already receiving a beta-blocker. **Elevated heart rate is linked to poor prognosis:** There is also now considerable clinical evidence of an association between an elevated resting heart rate and mortality in patients with coronary heart disease. Furthermore, studies have highlighted a resting heart rate of 70bpm, or greater, to be a threshold at which there is significantly increased risk of cardiovascular events in patients with pre-existing CAD[13-15]. **The value of heart rate in clinical practice:** Resting heart rate is an important cardiovascular parameter that can be simply and inexpensively measured and recorded. Routine measurement and recording of heart rate in clinical practice in all patients with stable angina can: • Simply assess the cardiovascular risk of a patient independent of other factors	

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						including blood pressure, cholesterol, and age.
						• Aid in rapid diagnosis of medical conditions, including life threatening arrhythmias, thyroid dysfunction or anaemia.
						• Help to optimise treatment by assessing:
						  • Response/adherence to rate limiting therapies
						  • Need for titration of heart rate limiting therapy
						  • Need for additional heart rate limiting therapy to be initiated
						
						The importance of heart rate control in angina is widely recognised:
						A variety of well respected societies recognise the importance of measuring heart rate when assessing and managing patients with coronary artery disease. This is reflected in the guidance provided in the publications of leading European and American associations:
						
						European Guidelines on cardiovascular disease prevention in clinical practice 2007 Practical Aspects: Heart Rate Management[16]
						"In the general population, avoidance of elevated heart rate through lifestyle	

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						measures can be recommended. These include regular physical activity, avoidance of psychological stress, and excessive use of stimulants such as caffeine. Pharmacological reduction of heart rate cannot be recommended in the asymptomatic population. Both β-blockers and selective If channel blockers are effective in the treatment of angina." AHA/ACC Guidelines for the Management of Stable Angina 2002[10]: "In the treatment of stable angina, it is conventional to adjust the dose of beta-blockers to reduce heart rate at rest to 55 to 60 beats per min. In patients with more severe angina, heart rate can be reduced to less than 50 beats per min provided that there are no symptoms associated with bradycardia and heart block does not develop." SIGN: Management of stable angina. 2007. Report No. 96[17]: "Doses should be tailored individually to ensure maximum beta-blockade depending on the sensitivity of the patient to the specific drug. Resting heart rate less than 60 beats per minute is an indication of beta-blockade".	

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						In line with these guidelines and for the purposes of optimising patient therapy we would like to suggest the recommendation that at least one rate-limiting anti-anginal be used when treating stable angina. **Heart rate control in practice could be improved:** Despite the evidence provided here, it is evident from a recent observational European study of almost 4000 patients with stable angina, that control of ischaemic symptoms through heart rate modification in patients is currently inadequate across both primary and secondary care[18]. In addition, a recent UK wide observational study concluded that a significant proportion of the patients with chronic stable angina undergoing elective PCI did not achieve therapeutic targets for HR control as well as lipids and BP. Over 50% of patients did not receive adequate heart rate lowering anti-anginal therapy to achieve recommended target resting heart rate[8]. **Role of blood pressure in the management of angina**: In addition to the important role heart rate plays in the treatment of stable angina, we would like to emphasise that blood pressure is also an important parameter to consider	

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						when treating and monitoring patients with stable angina. Raised blood pressure has been shown to be associated with the complex underlying pathophysiology of myocardial ischaemia[1,19] and over 60% of patients with angina have co-existing hypertension as shown by the European Heart Survey in 2006[20]. More importantly, many current anti-anginal therapies have a significant effect on blood pressure[21-24] and therefore would not be appropriate in patients where additional blood pressure reduction could have a detrimental effect[25-26]. In light of the evidence provided Servier would like to recommend that both heart rate and blood pressure, and the important roles they play in the selection and monitoring of appropriate patient-centred treatments for stable angina, be acknowledged within this guideline as outlined above. **References:** 1. Collins P, Fox KM. Pathophysiology of Angina. Lancet 1990; 335:94-96 2. Lang CC, Gupta D, Kalra P et al. Elevated heart rate and cardiovascular outcomes in patients with coronary artery disease: Clinical evidence and	

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						pathophysiological mechanisms. Atherosclerosis 2010; 212:1-8 3. Fox et al. Guidelines on the Management of Stable Angina Eur Heart J 2006; 27:1341-1381 4. Andrews T, Fenton T, Toyosaki N et al. Subsets of ambulatory myocardial ischemia based on heart rate activity. Circadian Distribution and Response to Anti-Ischemic Medication. Circulation 1993; 88:92-100 5. Pratt CR, McMahon RP, Goldstein S et al. Comparison of subgroups assigned to medical regimens used to suppress cardiac ischemia (the Asymptomatic Cardiac Ischemia Pilot [ACIP] Study). Am J Cardiology 1996; 77:1302-1309 6. Freedman SB, Wong CK. Triggers of daily life ischaemia Heart 1998; 80:489-492 7. Kop WJ, Verdino RJ, Gottdiener JS et al. Changes in Heart Rate and Heart Rate Variability Before Ambulatory Ischemic Events JACC 2001 Vol. 38, No.3 8. Elder DHJ, Pauriah M, Lang CC et al. Is there a Failure to Optimize theRapy in anGina pEcToris (FORGET) study? QJM 2010; 103(5):305-310 9. http://nobelprize.org/nobel_prizes/medicine/laureates/1988/black-lecture.pdf last	

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						accessed 31.01.11 10. Gibbons RJ, et al. ACC/AHA Practice Guidelines: Guideline update for the management of patients with chronic stable angina. 2002; 1-124 11. Tardif JC, Ford I, Tendera M et al. Efficacy of ivabradine, a new selective I(f) inhibitor, compared with atenolol in patients with chronic stable angina. Eur Heart J 2005; 26:2529-36 12. Tardif JC, Ponikowski P, Kahan T et al. Efficacy of the I(f) current inhibitor ivabradine in patients with chronic stable angina receiving beta-blocker therapy: a 4-month, randomized, placebo-controlled trial. Eur Heart J 2009; 30:540-8 13. Diaz A, Bourassa MG, Guertin M-C et al. Long-term prognostic value of resting heart rate in patients with suspected or proven coronary artery disease. Eur Heart J 2005; 26:967-974 14. Fox K, Ford I, Steg PG et al. Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a subgroup analysis of a randomised controlled trial. Lancet 2008; 372:817-821 15. Kolloch R, Legler UF, Champion A et al. Impact of resting heart rate on outcomes	

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						in hypertensive patients with coronary artery disease: findings from the International VErapamil-SR/trandolapril STudy (INVEST) Eur Heart J. 2008; 29:1327–1334 16. Graham I et al. European guidelines on cardiovascular disease prevention in clinical practice: Executive summary. Eur Heart J 2007; 28(19):2375–414 17. Scottish Intercollegiate Guidelines Network. Management of stable angina. NHS Quality Improvement Scotland; 2007. Report Number: 96 18. Daly CA, Clemens F, Lopez-Sendon JL et al. Inadequate control of heart rate in patients with stable angina: results from the Euro heart survey. Postgrad Med J. 2010; 86:212-217 19. Robinson BF. Relation of Heart Rate and Systolic Blood Pressure to the Onset of Pain in Angina Pectoris. Circulation 1967; 35:1073-1083 20. Daly CA, Clemens F, Lopez-Sendon JL et al. The impact of guideline compliant medical therapy on clinical outcome in patients with stable angina: findings from the Euro Heart Survey of stable angina. Euro Heart J 2006; 27:1298–1304 21. Bruce RA, Hossack KF, Kusumi F.	

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						Excessive reduction in peripheral resistance during exercise and risk of orthostatic symptoms with sustained-release nitroglycerin and diltiazem treatment of angina. Am Heart J. 1985; 109:1020-6 22. Boden WE, Korr KS, Bough EW. Nifedipine-induced hypotension and myocardial ischaemia in refractory angina pectoris. JAMA 1985 253(8):131-5 23. Crawford MH. Effectiveness of diltiazem for chronic stable angina pectoris. Acta Pharmacol Toxicol (Copenh)1985; 57 suppl 2:44-8 24. Thadani U, Rodgers T. Side effects of using nitrates to treat angina. Expert Opin Drug SAF. 2006; 5(5):667-74 25. http://www.medicines.org.uk/emc/medicines/24103/SPC/verapamil 26. http://www.medicines.org.uk/emc/medicines/23945/SPC/diltiazem+hydrochloride+tablets	
SH	Servier Laboratories	5	Full	50	1	For ease of use and clarity of the **algorithm,** we would like to suggest that some minor alterations be considered: *1.* Where the algorithm advises: "*symptoms not controlled – see next page"* we would suggest replacing this with "*where symptoms not controlled*	Thank you for your suggestion. We have altered the recommendations and this has also altered the algorithm.

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						after trial of two agents in optimal doses – see next page" This would ensure that the algorithm was in line with the text within the guideline **(Page 54, line 29)**: "*Offer people optimal drug treatment for the initial management of stable angina. Optimal drug treatment consists of one or two anti-anginal drugs as necessary plus drugs for secondary prevention of cardiovascular disease."* 2. This approach could also be considered for the left side of the diagram	
SH	Servier Laboratories	6	Full	120	1	**Table:** the RRR reported for BEAUTIFUL are not those cited in the publication: Fox KM, Ford I, Steg PG, et al. *Relationship between ivabradine treatment and cardiovascular outcomes in patients with stable coronary artery disease and left ventricular systolic dysfunction with limiting angina: a subgroup analysis of the randomized, controlled BEAUTIFUL trial.* Eur Heart J 2009; 30:2337-45: • Patients with limiting angina - CV death or hospitalisation for MI or HF - (follow-up median 18 months): RR 0.76 (0.58-1.00) is cited in publication not RR 0.77 (0.6 to 1) • Patients with limiting angina - all cause mortality (follow-up median 18 months): RR 0.87 (0.62-1.21) is cited in	Thank you for your comments. The results are reported in the BEAUTIFUL trial publication as hazard ratios and we have reported it as relative risk (RR). Hence there is a difference in the values.

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						publication not RR 0.88 (0.64 to 1.2) • Patients with limiting angina - Hospitalization for HF - (follow-up median 18 months): RR 0.84 (0.53-1.33) is cited in publication not RR 0.85 (0.54 to 1.33)	
SH	Servier Laboratories	7	Full	125	7	**Evidence statements** - **Fox 2009:** Where it is stated "*Evidence from one RCT shows that there was no statistically significant difference between ivabradine (7.5 mg) and placebo in patients with limiting angina for CV death or hospitalisation for MI or HF [RR 0.77 (0.6 to 1.0)]",* we would like this to be altered to *"Evidence from one RCT shows that there was a difference between ivabradine (7.5 mg) and placebo in patients with limiting angina for CV death or hospitalisation for MI or HF [RR 0.76 (0.58-1.00)], which was of borderline significance"* since the cited p-value was 0.05. This would show consistency with the statement on page 128, 7th paragraph, under the quality of evidence section where it is stated: "*The BEAUTIFUL trial assessed the effect of ivabradine in people with coronary artery disease and impaired left ventricular function. In a subgroup analysis of patients*	Thank you for your comment. In the evidence statements we state an outcome as statistically significant based on the relative risk (RR)/ mean difference (MD) and their respective CIs. The confidence intervals are more useful for clinical interpretation and drafting of recommendations than p values.

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						whose limiting baseline symptom was angina, ivabradine was associated with a reduction in the composite rate of the primary endpoint (cardiovascular death and hospitalisation for myocardial infarction or heart failure) of borderline significance".	
SH	Servier Laboratories	8	Appendix E2	General		In the interest of transparency, Servier are interested to know why the rationale behind the quality grading is provided for some studies and not others, specifically relating to sections: "What is the comparative clinical /cost effectiveness of standard anti-anginal drugs (beta blockers, calcium channel blockers) for the management of angina?" page 43 onwards and "What is the clinical/cost effectiveness of newer drugs for the management of angina?" page 72 onwards.	Thank you for your comment. The quality assessment reports for some questions about pharmacological interventions (Ivabradine, Ranolazine, Nicorandil and short acting nitrates) have been produced from an earlier version of our database which does not generate the quality grading in the same way. The grading/quality assessment in of all studies in the guideline have been conducted according to NICE methods. Moreover the quality of evidence reported in the GRADE table is generated by outcome rather than by study and is more important in development of recommendations than overall study quality.
SH	Servier Laboratories	9	Appendix E2	83 & 90		Servier are interested to know why the ASSOCIATE study - "Tardif JC, Ponikowski P, Kahan T, et al. *Efficacy of the I(f) current inhibitor ivabradine in patients with chronic stable angina receiving beta-blocker therapy: a 4-month, randomized, placebo-controlled trial.* Eur Heart J 2009; 30:540-8" is split between two gradings for evidence –	Thank you for your comment. This was an error and we have amended the gradings in the evidence tables accordingly.

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						Grade 1+ and Grade 1++. As this is one study, we feel it important to understand the rationale behind this.	
SH	Servier Laboratories	10	Full	55&56		Please note that the footnotes on this page do not correspond with the items to which they are referring.	Thank you for your comment. This has been amended accordingly.
SH	Society for Cardiothoracic Surgery	1				SCTS welcomes the opportunity to comment on the proposed NICE Guidelines for stable angina. From the outset we would emphasise that SCTS strongly supports the NICE principles and process. While the guidelines are extensive, covering 456 pages, **STCS will confine its remarks to those sections dealing with revascularisation**.	Thank you for your comments. We have structured our reply around the separate points made in the comment.
SH	Society for Cardiothoracic Surgery	2				1. TESTING FOR ISCHAEMIA **The proposed NICE Guidelines**: Under section 4.2 'Key priorities for Implementation' (page 52) it states "do not routinely perform tests for myocardial ischaemia or anatomical tests for obstructive coronary artery disease to stratify risk (1.2.3)". *SCTS COMMENT: We do not understand the rationale for this statement. The presence of demonstrable ischaemia (>10% of myocardial volume) is a well recognized risk factor for increased mortality. It is the demonstration of ischaemia or certain anatomic patterns of disease (eg tight left*	The GDG did not consider it appropriate to routinely recommend investigations without a clear indication that acting on the results of those investigations would improve outcome. The GDG agree that functional testing (for ischaemia) can indicate poor prognosis. The GDG did not agree that there was adequate evidence to recommend revascularisation on the basis of ischaemia alone. The GDG agreed that there is evidence that patients with certain anatomic patterns may benefit from revascularisation. The GDG considered

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						main stenosis or severe 3 vessel disease) that identifies those patients who have a prognostic benefit from revascularisation. Without this information how is it possible to decide whether a patient only requires optimal medical therapy or whether revascularization is also justifiable on prognostic grounds?	that the evidence for this comes from sub-group analyses of studies of surgical revascularisation versus medical therapy that were performed 30 years ago. These studies recruited predominantly symptomatic middle-aged men with good left ventricular function, and secondary prevention measures (antiplatelet agents, statins, RAS inhibitors) used routinely in contemporary practice were either not available or not used. Hence there is uncertainty about how applicable these studies are to modern treatment of cardiovascular disease. In the pathway in this guideline patients who remain symptomatic following drug treatment will be offered angiography, and if appropriate myocardial revascularisation. Following stakeholder consultation we have changed the recommendations to ensure that health care professionals inform patients whose symptoms are controlled on medical treatment that a subgroup may have anatomical disease for which treatment may have a prognostic benefit and that investigation should be considered for patients following this explanation.
SH	Society for Cardiothoraci	3				2. THE PROCESS AND CRUCIAL MISSING EVIDENCE	The development of NICE guidelines requires the GDG to specify outcomes of

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	c Surgery					**The proposed NICE Guidelines**: In terms of process the proposed NICE guidelines include a comprehensive review of the literature, similar to that reviewed by the 2010 ESC/EACTS guidelines on Myocardial Revascularization [1] and the 2009 Appropriateness of Coronary Revascularization guidelines from the USA [2]. *SCTS COMMENT: SCTS strongly supports this approach of a robust and detailed examination of the existing evidence. SCTS are therefore disappointed that two of the most important pieces of evidence regarding revascularization [2,3], including the most definitive meta-analyses of PCI and CABG ever undertaken [3], and which have profoundly different conclusions from those of the proposed NICE guidelines, have been omitted. An abstract of this meta-analyses [3] reporting that there is not only a survival advantage to revascularization over medical therapy but that the survival benefit is significantly greater with CABG is included:* The Impact of Revascularization on Mortality in Patients with Nonacute Coronary Artery Disease (Jeremias et al *The American Journal of Medicine (2009) 122, 152-161*	interest when comparing interventions. An evidence review is then undertaken to look specifically for evidence for those outcomes. Original meta-analyses are carried out as appropriate. The recommendations in the guideline are based on the clinical review carried out for the guideline and any relevant health economic analyses. Reference (2) is a report and is not included as it is not original research evidence. The meta-analysis by Jeremias et al (2009) (reference 3 in the references submitted) is not included as an original meta-analysis was performed for the guideline. All of the studies included in the meta-analysis by Jeremias et al (2009) were considered for inclusion but some were excluded from the meta-analysis done for this guideline and the reasons for exclusions are listed below. Most exclusions were because the study populations were not patients with stable angina which is the remit for this guideline. Patients with ACS have a different risk profile to patients with stable angina and impact of revascularisation may be different.

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						ABSTRACT BACKGROUND: Although early revascularization improves outcomes for patients with acute coronary syndromes, the role of revascularization for patients with nonacute coronary artery disease is controversial. The objective of this meta-analysis was to compare surgical or percutaneous revascularization with medical therapy alone to determine the impact of revascularization on death and nonfatal myocardial infarction in patients with coronary artery disease. METHODS: The Medline and Cochrane Central Register of Controlled Trials databases were searched to identify randomized trials of coronary revascularization (either surgical or percutaneous) versus medical therapy alone in patients with nonacute coronary disease reporting the individual outcomes of death or nonfatal myocardial infarction reported at a minimum follow-up of 1 year. A random effects model was used to calculate odds ratios (OR) for the 2 prespecified outcomes. RESULTS: Twenty-eight studies published from 1977 to 2007 were identified for inclusion in the analysis; the revascularization modality was percutaneous coronary intervention in 17 studies, coronary bypass grafting in 6	<u>Studies included in Jeremias et al (2009) and excluded from guideline meta-analysis with the reason for exclusion - in chronological order:</u> Norris et al (1981) - after recurrent MI TOPS (1992) - 4-14 days post thrombolytic treatment of MI Sievers et al (1993) - only abstract available (Full text not published) DANAMI (1997) - post MI. Dakik et al (1998) - post MI Horie et al (1998) - after q wave anterior MI Bech et al (2001) - designed to evaluate the role of pressure wire in patients referred for PCI. An ITT analysis of the entire randomised cohort has not been published. TOAT (2002) - after q wave anterior MI ALKK (2003) - No or minor angina post MI DECOPI (2004) - post first q wave MI Hambrecht et al (2004) - included in the guideline but the GDG considered it more appropriate to include this study in the review of exercise training and rehabilitation. OAT (2006) - 3-28 days post MI INSPIRE (2006) - post MI survivors SWISSI- II (2007) - recent MI

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						studies, and either strategy in 5 studies. Follow-up ranged from 1 to 10 years with a median of 3 years. The 28 trials enrolled 13,121 patients, of whom 6476 were randomized to revascularization and 6645 were randomized to medical therapy alone. The OR for revascularization versus medical therapy for mortality was 0.74 (95% confidence interval [CI], 0.63-0.88). A stratified analysis according to revascularization mode revealed both bypass grafting (OR 0.62; 95% CI, 0.50-0.77) and percutaneous intervention (OR 0.82; 95% CI, 0.68-0.99) to be superior to medical therapy with respect to mortality. Revascularization was not associated with a significant reduction in nonfatal myocardial infarction compared with medical therapy (OR 0.91; 95% CI, 0.72-1.15). CONCLUSION: Revascularization by coronary bypass surgery or percutaneous intervention in conjunction with medical therapy in patients with nonacute coronary artery disease is associated with significantly improved survival compared with medical therapy alone.	
SH	Society for Cardiothoracic Surgery	4				*Another limitation is including only the 1 year [4] but not the 3 year [5] results of the SYNTAX trial, which have been widely presented at major international meetings although not yet appeared in print. Failure to*	The three year results of SYNTAX are only available as an abstract. Following stakeholder consultation we have added reference to these results to the evidence to recommendations section and

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						even reference these results is unfortunate as SYNTAX is unquestionably the most important trial ever to compare the results of PCI and CABG in 'real life' practice. This is of particular relevance as only referencing the one year results of the SYNTAX trial [4] ignores the survival benefit of CABG which tends to accrue with time with more severe coronary artery disease (as confirmed in the three year results of SYNTAX [5]).	acknowledge how influential these are in the cardiology community. The GDG agree that SYNTAX is an important trial. The survival advantage with SYNTAX that is quoted appears to be confined to patients with high SYNTAX scores which is an unpublished subgroup analysis. Abstracts are not included in NICE guidelines as the guideline development process requires full assessment of the evidence to inform both clinical and health economic analyses. We have indicated to NICE the importance of this study and the need to review the guidance once the published results become available.
SH	Society for Cardiothoracic Surgery	5				3. FAILURE TO APPRECIATE OR ACKNOWLEDGE IMPORTANT FUNDAMENTAL LIMITATIONS OF THE LITERATURE **The proposed NICE Guidelines**: In the Introduction (page 24) the proposed NICE guidelines state that controversy applies "particularly to the role of revascularisation for which symptomatic but not prognostic benefit has emerged as a predominant finding in contemporary clinical trials" and "stimulated considerable debate about the role of percutaneous and surgical management strategies in these patients" and then cite the COURAGE [6], Bari 2D [7] and MASS II [8] trials to illustrate this point.	We acknowledge that the examples provided in the introduction were not appropriate examples of the point we wished to make and we have amended the introduction.

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						*SCTS COMMENT: The proposed NICE guidelines omit the most definitive meta-analyses [3] which reaches the opposite conclusion about the prognostic benefit of revascularization over medical therapy. Furthermore, none of the trials cited was actually designed to examine a primary end point of **survival benefit** between PCI and CABG:* • *COURAGE did not include CABG patients [6],* • *BARI 2D "was designed to compare coronary revascularization with intensive medical therapy, not to compare CABG with PCI" [7]* • *MASS II [8] had a composite end point of MACE including death, MI, unstable angina and repeat revascularization (ie was underpowered to detect mortality differences).*	
SH	Society for Cardiothoracic Surgery	6				*A further major and fundamental failure of the guidelines is the absence of any appropriate discussion of the limitations of many of the trials of PCI vs CABG with respect to routine clinical practice. It is well documented in the literature [9] that with the exception of the MASS II [8] and SYNTAX [4,5] trial* • *most trials only included fewer than 10% of potentially eligible patients,*	The GDG did discuss the limitations of the trials and considered that the limitations of the trials were reviewed in the Full guideline. We acknowledge that stakeholders have considered the discussion inadequate and we have added to the evidence to recommendations sections when discussing the choices between medical and revascularisation treatments and

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						the vast majority of whom had single or double vessel disease (and of whom only 40% actually had proximal LAD disease) and normal left ventricular function, a population in whom it was already well established that there was no prognostic benefit from revascularisation [10]. • *patients with known prognostic benefit of CABG ie those with 3 vessel disease, left main disease and especially in the presence of impaired ventricular function were largely excluded from the trials.* • *there is no mention of several large registries containing up to tens of thousands of propensity matched patients showing a clear survival benefit of CABG over PCI at 3 years of follow up with a seven fold reduction in repeat intervention [9]. These registries have the strength of reflecting real clinical practice although clearly have the potential for confounding in the absence of randomization. It is of interest however that their findings are identical to that for 3 vessel disease in the SYNTAX trial (which enrolled typical 'real-life' patients) at 3 years*	between PCI and CABG. This includes acknowledgement that recent trials of initial strategies of revascularisation versus medical therapy (e.g. COURAGE, BARI-2D, MASS-11) excluded patients with left main stem disease or impaired left ventricular function. We acknowledge that the wording of the recommendations was potentially misleading and we have clarified the intention of the GDG with regard to choice of revascularisation strategy. The recommendations relating to the choice between CABG and PCI apply to patients who are considered suitable for both procedures. The wordings of all the recommendations for revascularisation have changed following stakeholder comments. We acknowledge that trials of PCI versus CABG recruited highly selected patients (this also applies to the trials of CABG versus medical therapy that originally reported a survival benefit for CABG). We consider that MASS II and SYNTAX were also selective. MASS II enrolled 611 patients who were selected from a registry of 20769 patients referred for coronary arteriography. In SYNTAX 4337

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						ie a marked survival advantage and a marked reduction in repeat intervention for CABG in comparison to PCI [5]. *Consequently, with the exception of SYNTAX, most of the RCT patients are not typical of those who undergo CABG in contemporary practice and this is still true even of the contemporary COURAGE [6] and BARI 2D trials [7]. In COURAGE only 30% of patients had 3 vessel disease and only one-third of patients had proximal LAD disease; for BARI 2D the respective incidences of 3 vessel disease were 20% for the PCI group and 52% for the CABG group and fewer than 20% of all BARI 2D patients had proximal LAD disease.* ***Indeed the atypical nature of many of the patients included in these trials of PCI and CABG is eventually acknowledged on page 258 of the proposed NICE Guidelines where it is stated "the trial results therefore may not be generalisable to the wider population of people with stable angina and require cautious interpretation".*** ***Despite this warning, that is exactly what the guidelines then repeatedly do, by the consistent, but erroneous, assertion that PCI should be favoured over CABG*** *(see below).*	patients with 3 vessel or LMS disease were assessed for eligibility and 1800 were randomised, but we have no information about the total pool of patients with multi-vessel disease considered for revascularisation at the participating centres during the recruitment period. It is likely that SYNTAX patients are also a highly selected subgroup of the wider population of patients undergoing revascularisation in routine practice. The published one year findings (and unpublished three-year data) from SYNTAX show no difference for death between PCI and CABG, and in the pre-specified sub group of patients with LMS disease there was no difference between PCI and CABG for death or cardiac death. The longest available follow up is available from MASS11 and the 10 year data from MASS 11 was included in both meta-analysis and health economic model. Repeat revascularisation by PCI and/or CABG was also included in the economic model. The GDG recognises that several large registry studies have compared outcomes in patients revascularised by CABG or by PCI. As the stakeholder acknowledges

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						Likewise there is no reference to the frequent limited duration of follow up of the trials (although the benefits of CABG tend to accrue with time) or the high numbers of cross overs (mainly from PCI to CABG) which both discriminate against the benefit of CABG.	interpretation of these studies is confounded by potential imbalances in baseline characteristics between non-randomised groups.
SH	Society for Cardiothoracic Surgery	7				4. DRAWING THE WRONG CONCLUSIONS FROM THE EVIDENCE OF EFFICACY OF PCI VS CABG **The proposed NICE Guidelines**: The proposed NICE guidelines state "CABG is slightly more effective in relieving symptoms of stable angina in the longer term" and "repeat revascularisation may be necessary after either PCI or CABG and the rate is higher after PCI than CABG" (p260). Consequently the NICE guidelines state in section 4.2, Key Priorities for Implementation (page 52) "consider PCI in preference to CABG for people with single vessel disease, multi vessel disease including left main disease, and who have continuing symptoms despite optimal medical treatment and anatomy suitable for PCI." *SCTS COMMENT: These statements and recommendations are at complete odds with what the four most important pieces of evidence in the literature actually report:*	The recommendations for PCI and CABG were informed by the meta-analysis performed for the guideline and by a health economic analysis. We recognise that an initial PCI-based revascularisation strategy is associated with a higher requirement for repeat revascularisation than an initial surgical strategy. The trials of CABG versus PCI compared two initial treatment strategies in patients considered suitable for either strategy. The differences in clinical outcomes observed in these trials, including the requirement for additional revascularisation procedures, were considered by the GDG. A new cost-utility analysis was developed for the guideline which compared CABG and PCI as a revascularisation procedure for patients with angina who are eligible for both. This was based on the RCT data identified in the clinical review; the clinical

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							outcomes incorporated in the model were mortality, myocardial infarctions, repeat revascularisation, and presence of angina symptoms. Results found that CABG was not cost effective when compared to PCI; this conclusion was mostly driven by the high initial cost of CABG. We have acknowledged the limitations of the model and the lack of generalisability to patients who are suitable only for CABG or who are at a higher risk; the GDG has made recommendations considering these points. The health economic analysis concluded that an initial strategy of PCI is more cost-effective than an initial strategy of CABG in patients who are initially considered suitable for either revascularisation procedure. This conclusion was robust to a series of sensitivity analyses and informs the recommendations.
SH	Society for Cardiothoracic Surgery	8				• *The most definitive meta-analyses in the literature reports that CABG has a superior survival benefit over PCI in comparison to medical therapy [3]:* ***'A stratified analysis according to revascularization mode revealed both bypass grafting (OR 0.62; 95% CI, 0.50-0.77) and percutaneous intervention (OR***	The meta-analysis by Jeremias et al (2009) was not appropriate to the population covered in this guideline as discussed above. An original meta-analysis was conducted for the guideline.

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						0.82; 95% CI, 0.68-0.99) to be superior to medical therapy with respect to mortality.'	
SH	Society for Cardiothoracic Surgery	9				• *The second most important meta-analyses [11] reporting efficacy of PCI and CABG reports:* ***'Incidence of death , myocardial infarction or repeat revascularization was 36% for PCI and 20% for CABG (HR for CABG 0.52 (0.49-0.57) p<0.001)'***	We agree that Hlatky (2009) Individual Patient Data analysis (reference 11 in the references submitted) reports a hazard ratio as stated. The hazard ratio for death is 0.91 (0.82 – 1.02) p= 0.12 and death or myocardial infarction is 0.97 (0.88 – 1.06) p=0.47. The combined hazard ratio is driven largely by revascularization rates. The authors conclude that 'long term mortality is similar after CABG and PCI in most patient subgroups with multi-vessel disease so choice of treatment should depend on patient preferences for other outcomes'. The GDG considered that the choice between CABG and PCI involves a trade-off between the more invasive surgical procedure associated with a low requirement for repeat intervention, and the less invasive percutaneous procedure associated with a higher risk of repeat intervention. The recommendations are also informed by the health economic analysis developed for the guideline.
SH	Society for Cardiothoracic Surgery	10				• *MASSII [8] '****Conclusions: PCI was associated with an increased need for further revascularization, a higher incidence of myocardial***	We agree with the conclusions listed for MASS II and acknowledge that in all studies there is a lower rate of revascularization following CABG than

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						infarction, and a 1.46-fold increased risk of combined events compared with CABG. Additionally, CABG was better than MT at eliminating anginal symptoms.	following PCI. In MASS II there was no significant difference in mortality between PCI and CABG groups at 10 years.
SH	Society for Cardiothoracic Surgery	11				• *SYNTAX [4,5]: '**CONCLUSIONS: CABG remains the standard of care for patients with three-vessel or left main coronary artery disease, since the use of CABG, as compared with PCI, resulted in lower rates of the combined end point of major adverse cardiac or cerebrovascular events at 1 year.** (ClinicalTrials.gov number, NCT00114972.)'*	The conclusions of SYNTAX are informed by the choice of endpoint. The recommendations in the guideline were informed by clinical and cost effectiveness analysis carried out for the guideline and the deliberations of the GDG.
SH	Society for Cardiothoracic Surgery	12				*SCTS COMMENT: SCTS is perplexed and concerned by the constant tendency of the NICE writing group to draw wrong conclusions from or misrepresent the trial data and, despite the proven superior efficacy of CABG, repeatedly recommend that PCI should be favoured over CABG. Not only is there not a shred of evidence to support this recommendation but it is actually at odds what the evidence consistently shows. In particular the statement "consider PCI in preference to CABG.." is, in effect, an open ticket to submit many patients to a demonstrably*	We agree that an initial revascularisation strategy of CABG is a more effective method of reducing the requirement for repeat revascularisation than an initial strategy of PCI. We disagree that PCI is a demonstrably less effective treatment with respect to a range of other clinical outcomes. We have altered the wording of the recommendations to indicate more clearly which people each recommendation refers to. The GDG used consensus to develop wording that should ensure

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						*less effective treatment**. In certain situations such as severe 3 vessel disease and complex left main- where an individual cardiologist considers the 'anatomy suitable' for PCI (as NICE recommends that discussion with a cardiac surgeon need only be considered but is not mandatory) this is a potentially very dangerous recommendation**.	adequate discussion occurs when anatomy is complex. In particular the GDG modified the recommendations for patients with more complex coronary anatomy, recognising that this group will have been excluded from trials and that based on older trials CABG has been shown to have a prognostic advantage.
SH	Society for Cardiothoracic Surgery	13				5. RELATIONSHIP OF NICE GUIDELINES TO OTHER CONTEMPORARY GUIDELINES ON MYOCARDIAL REVASCULARIZATION **The proposed NICE Guidelines:** The trials and studies reviewed by NICE were also reviewed by a combined committee of the European Society of Cardiology and the European Association of Cardiothoracic Surgery, the 'ESC/EACTS guidelines on myocardial revascularization 2010' [1] and by ACCF/SCAI/STS/AATS/AHA/ASNC 2009 Appropriateness Criteria for Coronary Revascularization [2]. *SCTS COMMENT: It is striking that the ESC/EACTS guidelines [1] and the ACRE recommendations [2] reviewing the same data reached completely different conclusions about the relative merits of CABG and PCI as shown in Table 9 of the ESC/EACTS guidelines and Figure 5 of the*	The membership of the guideline group is agreed with NICE and discussed with stakeholders at a public Stakeholder workshop. Written submissions from stakeholders during the scoping period also informs the membership of the guideline group. Members of NICE guideline groups do not represent organisations. The group includes staff of the National Clinical Guideline Centre who provide independent research and health economic analysis. The group includes patient representatives who provide a unique perspective on the trade-offs between the risks and benefits of different treatment strategies. The ESC/EACTS guidelines do not consider the cost effectiveness of different revascularisation strategies and do not include patient representatives. Moreover

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						ACRE recommendations. The most likely explanation for this difference is that the ESC/EACTS guidelines were written by a team of 25 clinician experts in the management of coronary disease but with a balanced committee of 8 non interventional cardiologists, 9 interventional cardiologists and 8 cardiac surgeons, who consequently managed to avoid several of the pitfalls in the proposed NICE guidelines. Likewise the ACCF/SCAI/STS/AATS/AHA/ASNC 2009 Appropriateness Criteria for Coronary Revascularization [2] were produced by the leading cardiology and cardiac surgery societies of the USA, but again with a balanced number of interventional cardiologists and cardiac surgeons. *It is also noteworthy that the 2010 ESC/EACTS guidelines have been strongly supported in a recent editorial in Heart [12] co-authored by XXXX, XXXX, XXXX and XXXX.*	we disagree that the ESC/EACTS guidelines '*reached completely different conclusions about the relative merits of CABG and PCI*'. In section 6.7 the ESC/EACTS guidelines state that: 'Current best evidence shows that revascularization can be readily justified: (i) on symptomatic grounds in patients with persistent limiting symptoms (angina or angina equivalent) despite OMT and/or (ii) on prognostic grounds in certain anatomical patterns of disease or a proven significant ischaemic territory (even in asymptomatic patients). Significant LM stenosis, and significant proximal LAD disease, especially in the presence of multivessel CAD, are strong indications for revascularization. In the most severe patterns of CAD, CABG appears to offer a survival advantage as well as a marked reduction in the need for repeat revascularization, albeit at a higher risk of CVA, especially in LM disease.'
SH	Society for Cardiothoracic Surgery	14				6. CONSISTENTLY UNBALANCED NATURE OF THE PROPOSED GUIDELINES **The proposed NICE Guidelines:** Another example of this biased approach in favour of	NICE clinical guidelines are required to include cost effectiveness analysis as well as clinical effectiveness. This has been outlined above.

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						PCI is that even if there was genuine equipoise between the revascularization strategies (and like the ESC/EACTS and ACRE guidelines SCTS believes that the evidence actually shows superiority of CABG in many situations) the guidelines state "consider PCI in preference" to CABG.	
SH	Society for Cardiothoracic Surgery	15				*SCTS comment: SCTS strongly disagrees with this NICE recommendation. Instead SCTS robustly endorses the concepts of transparency, real patient choice and genuine informed consent and believes that it is axiomatic that if there is equipoise between treatments patients should be given the option of both treatments. The NICE guideline writing group also appear to be oblivious of strong evidence from the literature that when patients are consented for interventions by an interventional cardiologist rather than a multidisciplinary team patients are often unlikely to understand the rationale for the procedure and far more likely to receive treatment NOT recommended by guidelines [13,14]. Indeed the recent white paper 'Liberating the NHS' emphasises the importance of the patient being at the centre of the decision making process and underpins the concept of 'Not about us without us'. Instead the NICE guidelines appear to promote the denial of real patient choice. It is for these*	We have distinguished between the need for multi-disciplinary team meetings to discuss choice of revascularisation strategy and information provision and discussion with patients. The GDG did not consider it appropriate that all patients suitable for revascularisation should be discussed at a multi-disciplinary team meeting. We have altered the recommendation to more clearly indicate which groups of patients we considered should be discussed. All NICE guidelines are developed using a principle of patient-centred care. We agree that patients should be given appropriate and balanced information on risk, benefits and limitations of procedures and have made recommendations listing some of the important aspects of treatments that the GDG considered should be explained to patients. The process of providing information to

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						reasons SCTS supports the ESC/EACTS Guideline recommendations that in situations where revascularisation is an option, then with few exceptions, this should be agreed by a multidisciplinary team underpinned by appropriate guidelines. SCTS are especially uneasy at what appears to be an unbalanced interpretation of the literature whereby ***the NICE Guideline Committee consistently recommend that the less effective treatment should be considered the preferable treatment.***	patients and explaining risk is complex and who provides the information for an individual patient is beyond the scope of a guideline. The ESC/EACTS guideline emphasizes the importance of multidisciplinary team but states that 'Guidelines may be used to avoid the need for systematic case-by-case review of all diagnostic angiograms' and recognises the concept of 'ad-hoc' percutaneous coronary intervention without prior multidisciplinary team discussion.
SH	Society for Cardiothoracic Surgery	16				<u>7. THE NICE GUIDELINE DEVELOPMENT GROUP</u> **The proposed NICE Guidelines**: The Guideline Development Group had 13 members including 4 Consultant Cardiologists, 2 General Practitioners with a special interest in Cardiology, **a single surgeon,** a Consultant Cardiac Radiologist, Cardiac Pharmacist, Cardiovascular Clinical Team Leader, Angina Nurse Specialist and 2 lay members. *SCTS COMMENT: This composition causes immediate concern with regards to recommendations for revascularization strategies by PCI or CABG. It is well known from previous European and North*	The GDG was tasked with developing a guideline for the management of patients with stable angina. As discussed above membership of the GDG is agreed with NICE and discussed at a public stakeholder workshop. Members of NICE guideline groups do not represent organisations. The group included a variety of clinical staff involved in the management of patients with angina, staff from the National Clinical Guideline Centre, and patient representatives. Myocardial revascularisation forms an important part of the management of patients with stable angina, but the guideline group was convened to develop a guideline that covered all relevant

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						American guidelines that guideline groups containing a heavy preponderance of cardiologists, and particularly interventional cardiologists, with a single 'token' cardiac surgeon have invariably favoured PCI over CABG even in the absence of an appropriate evidence base. Recognizing this inherent flaw in guideline groups without equal representation of appropriate expert opinions, the current 2010 ESC/EACTS guidelines on Myocardial Revascularization [1] were produced by a balanced writing committee of equal numbers of non interventional cardiologists, interventional cardiologists and cardiac surgeons as were the Appropriateness of Coronary Revascularization guidelines from the USA [2]. SCTS wonders if the composition of the NICE writing group may have contributed to its many examples of erroneous representation of the evidence and its seriously flawed recommendations.	aspects of the management of patients with stable angina.
SH	Society for Cardiothoracic Surgery	17				8. SCTS CONCLUSIONS REGARDING THE PROPOSED NICE GUIDELINES With regards to recommendations for revascularization, SCTS believe that the proposed guidelines have excluded important data, consistently misinterpreted or misrepresented other data and have reached conclusions and made	Thank you for your comment. We have considered the comments made by stakeholders and changed some of the recommendations as part of that response. Our response to individual points summarised here are outlined above.

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						recommendations inconsistent with the evidence presented. Likewise their recommendations for revascularization are at serious odds with the most prestigious guidelines from Europe and the USA. In the view of SCTS, the recommendation that an individual cardiologist can consider PCI treatment for even severe three vessel or left main disease if they consider the 'anatomy suitable' is at complete odds with the evidence, undermines the concept of the multidisciplinary team and most worryingly is a potentially dangerous recommendation. Accordingly SCTS does not support these guidelines and recommends a major re-writing in a more balanced and objective fashion. Indeed we are so concerned by both the omission of key evidence accompanied by misinterpretation and/or misrepresentation of other data leading to potentially dangerous recommendations that we have copied our concerns to XXXX, XXXX, XXXX, XXXX and XXXX. 9. REFERENCES 1: European Association for Percutaneous Cardiovascular Interventions, Wijns W, Kolh P, Danchin N, et al; Guidelines on myocardial revascularization: The Task	

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						bypass grafting for severe coronary artery disease. N Engl J Med. 2009 Mar 5;360(10):961-72. 5. Mohr FW. SYNTAX 3VD: Three-Year Outcomes from a Prospective Randomized Trial of Paclitaxel-Eluting Stents Compared to Bypass Graft Surgery in Patients with Triple Vessel Coronary Artery Disease. Washington: TCT, 2010. 6: Boden WE, O'Rourke RA, Teo KK, et al ; COURAGE Trial Research Group. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med. 2007 Apr 12;356(15):1503-16. 7: BARI 2D Study Group, Frye RL, August P, Brooks MM, et al A randomized trial of therapies for type 2 diabetes and coronary artery disease. N Engl J Med. 2009 Jun11;360(24):2503-15. 8: Hueb W, Lopes N, Gersh BJ, et al Ten-year follow-up survival of the Medicine, Angioplasty, or Surgery Study (MASS II): a randomized controlled clinical trial of 3 therapeutic strategies for multivessel coronary artery disease. Circulation.2010 Sep 7;122(10):949-57. 9: Taggart DP. Thomas B. Ferguson Lecture. Coronary artery bypass grafting is still the best treatment for multivessel and left main disease, but patients need to	

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						Cardiology/American Heart Association guidelines for percutaneous coronary interventions and coronary artery bypass graft surgery: what happens in actual practice? Circulation. 2010 Jan 19;121(2):267-75.	
SH	Society for Cardiothoracic Surgery in Great Britain & Ireland	1	Full	General		**SCTS: DETAILED RESPONSE TO PROPOSED NICE GUIDELINES**	
SH	St Jude Medical UK Ltd	1	Full	gen		I have attached a number of clinical articles supporting the evidence of efficacy of this therapy. The SPIRIT Trial flies against all the previous studies on cost effectiveness of SCS therapy because it measures different parameters. The advent of rechargeable stimulators has dramatically reduced the long-term costs of this therapy by reducing the frequency of battery replacements and replacement surgeries and associated costs  Parker 2004.pdf  Norrsell 1997.pdf  Wei Yu Presentation.pdf  Taylor Review of Econ SCS Final 1905(	Thank you for your comment and information. Evidence for the use of Spinal Cord Stimulation was not reviewed for the guideline. Spinal Cord Stimulation has been reviewed as part of a NICE Technology Appraisal (TA159) which has concluded 'Spinal cord stimulation is not recommended as a treatment option for adults with chronic pain of ischaemic origin except in the context of research as part of a clinical trial'.

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						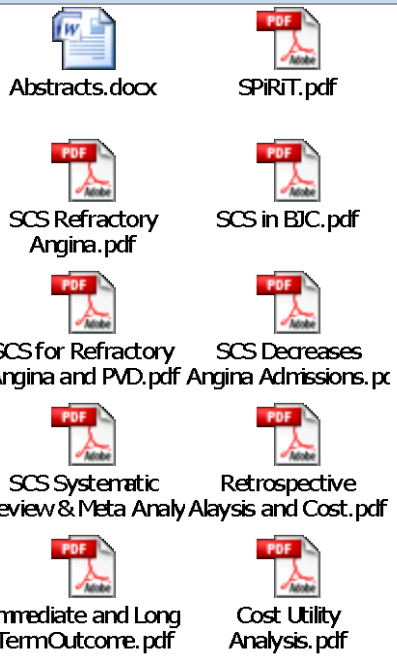	
SH	SW London Cardiac and Stroke Network	1	Nice	7	1.48	You recommend PCI as the preferred option for revascularisation for left main stem disease and multi-vessel disease – most studies suggest CABG has a better long term outcome.	Thank you for your comment. The wording of the recommendation indicates that PCI should be considered if anatomy is suitable for PCI, not that it is always the preferred option. We accept that it has been standard advice that CABG has better long term outcomes for LMS disease and three vessel disease. This interpretation is challenged by more recent studies and depends on choice of outcomes. The results from the SYNTAX

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							trial at one year indicate no significant difference between CABG and PCI for death, CVA, or revascularisation for people with LMS disease. The Hlatky IPD meta-analysis of patients with multi-vessel disease does not show a significant difference for death at a median follow up of 5.9 years. Revascularisation rates are greater following PCI than CABG. The cost effectiveness analysis conducted for this guideline suggests that PCI is a more cost-effective strategy than CABG for patients considered suitable for either revascularisation strategy, including patients with left main stem and multivessel disease.
SH	SW London Cardiac and Stroke Network	2	Nice	12	1.3.10	You recommend monotherapy with long-acting nitrates, Ivabradine, Nicorandil and ranolazine without a specific assessment of the costs of each option – nitrates is the most cost effective option and should be the preferred strategy	Thank you for your comment. The recommendation does include the need to consider costs as well as other factors. Evidence on comparative effectiveness of these drugs was not adequate to assess the cost-effectiveness. As the cheapest option may not be the most cost-effective option, the GDG preferred not to base the recommendations simply on costs.
SH	The Royal College of Physicians	1	Full	gen		The Royal College of Physicians wishes to endorse the response submitted by the British Cardiovascular Society to this guideline consultation.	Thank you for your comment.
PR	XXXX	1	NICE	general	General	Due to time constraints I have concentrated on the short (NICE) version and referred to	Thank you for your comments. The guideline presumes that diagnosis will

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						the full draft in specific areas only. Please accept my apologies if the issues I have raised have been addressed elsewhere within the full guideline. The short guideline is at times ambivalent. This may well stem from a desire to avoid straying into either CG95 or technology appraisal 73 but lends some ambiguity to the recommendations in so far as 1.2.3 specifically says do not routinely perform functional or anatomical tests yet 1.4.3 suggests that coronary angiography should be offered to guide the revascularisation strategy if not recently completed. Does this guideline assume that prior objective confirmation of CAD has occurred – if so should this be stated in the Introduction? I understand the evidence base and note the comments (p 325 full), but as presented the recommendation (1.2.3 – a KPI) is bald, non specific and lacks context. Should there a) be clarification that this applies to patients with confirmed CAD (if that is the intent) and b) that these tests should not be done to evaluate prognostic benefit from revascularization.	have taken place in line with NICE Guideline 'Chest pain of recent onset'. This recommends that diagnosis is made on clinical grounds or using functional or anatomical testing depending on likelihood of the coronary artery disease. We have altered recommendation 1.2.3 following stakeholder comment. The guideline presumes diagnosis has taken place according to NICE guideline 'Chest pain of recent onset'. We have added a recommendation to inform readers that diagnosis is covered in that guideline. The recommendations on further investigation and treatment are appropriate for people with an inherited diagnosis of angina. The advice regarding different types of CCBs related to licensing and side effect issues and not to efficacy. The evidence review did not find different efficacy for dihydropyridine and non- dihydropyridine CCBs. The information quoted comes from the SPC of the drugs and we have added this information to the evidence to

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						Should the Introduction clarify whether patients treated according to this guidance will have had previous functional or anatomical assessment. If it does how does this guidance apply to a patient who may have an "inherited" diagnosis of stable angina which is clinically appropriate but for whom formal diagnostic assessment has never been done? Specific mention is made in the text to dihydropyridine CCBs (footnote 1 p12, footnote 4 p13) yet in the evidence section of the long guideline I could not find any particular distinction made between dihydropyridine and non- dihydropyridine CCBs – see comment 6 below. Will this be understood by a broader readership? Is clarification required in both long and short texts?	recommendations in each section
PR	XXXX	2	NICE	5	7	The word "both" is unclear – consider suitable for "both percutaneous revascularisation or coronary artery bypass surgery".	Thank you for your comment. We have made this change to the wording.
PR	XXXX	3	NICE	7	5	Is the meaning of "pacing" activities sufficiently clear to all possible readers?	Thank you for your comment. The NICE guideline is directed to healthcare professionals and the GDG considered that the term would be clear to readers. We will work with the editors on the wording.
PR	XXXX	4	NIC	7	8, 9	(see general comments above) I have read	Thank you for your comment. This

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			E			the evidence section. Is it assumed that prior diagnostic imaging or assessment has been performed/	guideline does not deal with diagnosis and this is covered in another NICE guideline 'Chest pain of recent onset'.
PR	XXXX	5	NICE	7	16ff (1.4.6 KPI)	If a multidisciplinary approach is to be encouraged is "considering" such an approach adequate or should this be "offered" (to all?)	Thank you for your comment. We have altered the wording of this recommendation to indicate more clearly which people should be discussed. The GDG did not consider that all people for whom revascularisation might be suitable should be discussed at an MDT.
PR	XXXX	6	NICE	7	20ff (1.4.7 KPI)	If there is ambivalence over superiority (comments on p 258) is "considering" such an approach adequate or should this be "offered" (to all?)	Thank you for your comment. We have altered the wording of this recommendation to indicate more clearly which people should be discussed. The GDG did not consider that all people for whom revascularisation might be suitable should be discussed at an MDT.
PR	XXXX	7	NICE	12	5/6/7 (1.3.6)	There is no specific mention of rate limiting calcium antagonists although diltiazem is widely used. The Evidence statement (p 92) appears not to cover this area (although a study finding equivalence of verapamil SR and atenolol is cited, the potential hazard of short acting CCB mentioned and two of three CCBs listed as studied are rate-limiting). Is the generic recommendation of a "calcium channel blocker" sufficiently precise?	Thank you for your comment. The evidence review did not indicate that one type of CCB was preferred over another when compared with BB. The issues arise only when CCBs are combined with other drugs.
PR	XXXX	8	NICE	12	11/12/13	Is this recommendation clear in context of preceeding recommendation regarding	Thank you for your suggestion. We have altered this recommendation following

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					(1.3.8)	intolerance of BB or CCB. (1.3.7) Consider altering to "if the person's symptoms are not controlled *on one medication*, consider either switching to the other option (calcium channel blocker or beta blocker if *tolerated)* or using a combination of the two"	stakeholder comment.
PR	XXXX	9	NICE	12	14/15 (1.3.9)	Is this necessary given 1.3.6?	Thank you for your comment. The GDG considered it important to make a recommendation not to use other drugs given the lack of evidence for their use.
PR	XXXX	10	NICE	13	8,9 (1.3.11)	Note footnote reference numbers for ivabradine and nicorandil are transposed from full draft.	Thank you for this information.
PR	XXXX	11	NICE	13	24	Is this footnote internally consistent? The footnote states: "Ivabradine should only be combined with a dihydropyridine CCB". Lines 9/10 p118 full guideline states: "Ivabradine is licensed for the treatment of angina in patients in sinus rhythm in combination with a BB" For clarity should the footnote read: "Concomitant use of ivabradine with heart rate reducing CCB such as verapamil or diltiazem is not recommended by the manufacturers". (as stated in full guideline p129)	Thank you for your comment. We have altered the wording of the footnote.

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