

openheart Comparison between National Institute for Health and Care Excellence (NICE) and European Society of Cardiology (ESC) guidelines for the diagnosis and management of stable angina: implications for clinical practice

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ABSTRACT

Cardiologists in the UK use clinical practice guidelines from the National Institute for Health and Care Excellence (NICE) and from the European Society of Cardiology (ESC) to aid clinical decision-making. This review compares their recommendations regarding stable angina. NICE's diagnostic algorithm changed clinical practice in the UK, with most cardiologists moving from the exercise ECG towards newer, more accurate imaging modalities such as CT and MRI for diagnostic testing in patients with a low or medium probability of coronary artery disease (CAD), and directly to invasive coronary angiography in patients with a high probability of CAD. ESC guidelines are based around stress imaging for most patient groups. Both guidelines stress the importance of optimal medical therapy for patients with stable angina. NICE recommends coronary artery bypass graft surgery to improve prognosis for patients with left main stem and/or proximal 3-vessel disease, whereas the ESC also includes proximal left anterior descending artery disease among its indications for revascularisation to improve prognosis, particularly if there is evidence of myocardial ischaemia. The relation between disease complexity and 5-year clinical outcomes after revascularisation in patients with left main stem and/or 3-vessel CAD has been integrated into ESC guidance through the use of the SYNTAX score to aid treatment selection in this group of patients. Patients with stable angina who have disease involving the proximal left anterior descending artery are less likely to undergo myocardial revascularisation if they are managed according to NICE's guidance compared with the ESC's guidance.

INTRODUCTION

The clinical practice guidelines most relevant to cardiologists in the UK are those produced by the National Institute for Health and Care Excellence (NICE) and the

European Society of Cardiology (ESC). Contemporary guidance is based on the same (or a very similar) evidence base, yet recommendations from the two bodies may differ. The aim of this review was to compare the main recommendations from NICE and the ESC regarding the management of stable angina.

COMPARISON OF GUIDELINES

Guideline development

NICE published separate guidelines for diagnosis in 2010, and for the management of stable angina in 2011 (table 1).^{1 2} Its recommendations regarding lipid modification and hypertension are specified in its own (separate) guidelines in these areas, both of which have been updated since the publication of the NICE guidance on stable angina.^{3 4} The ESC guidance incorporates diagnosis and management into a single document, which was published in 2013.⁵ It refers to its own guidelines on myocardial revascularisation, which were updated in 2014.⁶

NICE includes in its diagnostic guideline adults with or without a prior diagnosis of cardiovascular disease who have recent onset chest pain suspected to be stable angina. Its management guideline is for adults who have been diagnosed with stable angina due to atherosclerotic disease. The ESC guidance incorporates a broader group which also includes patients with asymptomatic coronary artery disease (CAD) and low-risk acute coronary syndromes.

In its guideline development, NICE posed 'key clinical questions', undertook a review of the relevant literature, critically appraised

Table 1 Summary of methodology used in the development of the clinical practice guidelines for the management of stable angina/stable coronary artery disease from NICE and the ESC

	NICE	ESC
Description	Two separate guidelines for diagnosis and management	Single guideline for diagnosis and management
Publication date	March 2010 (diagnostic); July 2011 (management)	August 2013
Literature search date	To April 2009 (diagnostic); to 22 October 2010 (management)	Not stated
Inclusions	<p><i>Diagnostic guidelines:</i></p> <ul style="list-style-type: none"> ▶ Adults with recent onset chest pain of suspected cardiac origin with or without a history of cardiovascular disease <p><i>Management guidelines:</i></p> <ul style="list-style-type: none"> ▶ Adults aged >18 years with stable angina due to atherosclerotic disease ▶ People with anginal symptoms and normal or minimally diseased coronary arteries 	<p>Stable angina</p> <p>Asymptomatic patients with known CAD</p> <p>Low-risk acute coronary syndrome patients (no ongoing chest pain, negative cardiac biomarkers, and a normal ECG)</p> <p>Asymptomatic patients with an abnormal test</p> <p>References made to microvascular dysfunction and coronary vasospasm</p>
Exclusions	<p><i>Diagnostic guidelines:</i></p> <ul style="list-style-type: none"> ▶ Non-ischaemic chest pain ▶ Management of CAD once diagnosis made <p><i>Management guidelines:</i></p> <ul style="list-style-type: none"> ▶ Recent onset chest pain ▶ Acute coronary syndromes ▶ Angina due to non-cardiac disease e.g. anaemia or non-coronary cause e.g. aortic stenosis, hypertrophic cardiomyopathy 	Not defined
Cost effectiveness	An intervention was defined as cost effective if it was both less costly in resource use and more clinically effective compared with all relevant alternative strategies, or if it cost <£20 000 per quality-adjusted life year gained compared with the next best strategy	Not assessed
Guidance	Simple statements	Statements usually associated with class of recommendation (I, IIa, IIb or III)* and level of evidence (A, B or C)†

*I—is recommended; IIa—should be considered; IIb—may be considered; III—is not recommended.

†A—multiple randomised controlled trials or meta-analyses; B—single randomised controlled trial or large non-randomised studies; C—consensus of opinion and/or small studies/retrospective studies/registries.

CAD, coronary artery disease; ESC, European Society of Cardiology; NICE, National Institute for Health and Care Excellence.

the quality of evidence, and made recommendation statements. The ESC made recommendations supported by a class of recommendation and level of evidence. Analyses of health economic data were considered by NICE but not by the ESC.

Diagnosis

Both NICE and the ESC recommend a clinical assessment which includes a history and physical examination. If the pain is non-anginal (one or no features of anginal pain), angina is excluded and other causes for the pain should be sought (table 2). If angina cannot be diagnosed or excluded based on the history (two or three features of anginal pain), then an ECG should be performed, and further diagnostic testing may be indicated depending on the pretest probability (PTP) of CAD. This is assessed from prevalence estimates of obstructive CAD based on age, gender and symptomatology

(table 3, web addendum table 1). Both guidelines recommend against diagnostic testing in patients who have a very low or very high PTP of CAD due to the limited added value of testing in these groups.

Table 2 Clinical classification of chest pain used by the National Institute for Health and Care Excellence and the European Society of Cardiology

Characteristics of angina:

- ▶ constricting discomfort in the chest, neck, shoulders, arms or jaw
- ▶ provoked by physical exertion or stress
- ▶ relieved by rest and/or nitrates within minutes

Typical angina:	Atypical angina:	Non-anginal pain:
All three characteristics present	Two characteristics present	One or no characteristics present

Table 3 Prevalence estimates for coronary artery disease in patients with stable chest pain based on age, gender and symptoms, and their influence on diagnostic testing**(a) NICE**

Age (years)	Non-anginal chest pain				Atypical angina				Typical angina			
	Men		Women		Men		Women		Men		Women	
	Lo	Hi	Lo	Hi	Lo	Hi	Lo	Hi	Lo	Hi	Lo	Hi
35	3	35	1	19	8	59	2	39	30	88	10	78
45	9	47	2	22	21	70	5	43	51	92	20	79
55	23	59	4	25	45	79	10	47	80	95	38	82
65	49	69	9	29	71	86	20	51	93	97	56	84

For men aged >70 years with atypical or typical angina, assume an estimate >90%.

For women aged >70 years, assume an estimate of 61–90% except women at high risk and with typical angina where a risk of >90% should be assumed.

Values are per cent of people at each mid-decade age with significant coronary artery disease.

Hi=high risk, diabetes mellitus, smoking and hypercholesterolaemia (total cholesterol >6.47 mmol/L).

Lo=low risk, none of these three.

Modified from NICE Guideline for the Diagnosis of Chest Pain of Recent Onset, 2010.

(b) ESC

Age (years)	Non-anginal chest pain		Atypical angina		Typical angina	
	Men	Women	Men	Women	Men	Women
35	18	5	29	10	59	28
45	25	8	38	14	69	37
55	34	12	49	20	77	47
65	44	17	59	28	84	58
75	54	24	69	37	89	68
85	65	32	78	47	93	76

Values are per cent of people at each mid-decade age with significant coronary artery disease.

Modified from ESC Guideline for the Management of Patients with Stable Coronary Artery Disease, 2013.

Recommended diagnostic testing

	Non-anginal chest pain—no diagnostic testing required (NICE)
	PTP for CAD below the threshold for diagnostic testing
	CT calcium score ± CT coronary angiogram
	Non-invasive stress imaging
	Exercise ECG where non-invasive stress imaging not available
	Invasive coronary angiogram
	PTP for CAD high—no diagnostic testing required

CAD, coronary artery disease; ESC, European Society of Cardiology; NICE, National Institute for Health and Care Excellence; PTP, pretest probability.

In NICE's guidance, patients who remain in the diagnostic algorithm fall into three groups which undergo different diagnostic testing according to the PTP of CAD:

- ▶ PTP 10–29%—CT calcium score with or without CT coronary angiography
- ▶ PTP 30–60%—functional imaging
- ▶ PTP 61–90%—invasive coronary angiography

NICE recommends against using the exercise ECG to diagnose or exclude stable angina for people without known CAD.

According to ESC guidance, if angina has not been excluded following clinical assessment, an echocardiogram should be performed. Patients who have both a left ventricular ejection fraction (LVEF) <50% and typical

angina should be offered invasive coronary angiography. Other patients who have a PTP of 15–85% should undergo non-invasive testing for ischaemia or CT coronary angiography. Stress imaging is the preferred option, but exercise ECG testing is recommended for patients with a PTP of 15–65% where stress imaging is not locally available. The ESC recommends against using the exercise ECG as a diagnostic test in patients with a PTP >65%. CT coronary angiography is recommended as an alternative to stress imaging in patients with a PTP 15–50%.

General considerations and lifestyle management

NICE recommends that men and women with symptoms of stable angina should be investigated and treated no differently (web addendum table 2).

The ESC includes recommendations regarding influenza vaccination, hormone replacement therapy, and a target for HbA1c in people with diabetes, areas which are not covered by NICE, and it makes more specific recommendations than NICE about body mass index, diet and exercise.

NICE recommends a target blood pressure of <140/90 mm Hg in patients aged <80 years and <150/90 mm Hg in those aged ≥80 years.⁴ The ESC recommends lowering blood pressure to <140/90 mm Hg irrespective of age, and to <140/85 mm Hg in patients with diabetes.

The ESC states that cardiac rehabilitation should be considered for all patients with CAD, whereas the

clinical and cost-effectiveness of cardiac rehabilitation in patients with stable angina is considered unproven by NICE.

Pharmacological management

Both NICE and the ESC recommend β -blockers and/or calcium channel blockers as first-line antianginal therapy, with long-acting nitrates, ivabradine, nicorandil or ranolazine reserved for patients who have contraindications to these agents or who fail to tolerate them (table 4). The ESC recommends the use of β -blockers in asymptomatic patients with large areas of ischaemia, a group not covered by NICE.

Low-dose aspirin is recommended in all patients with stable angina/CAD for the secondary prevention of cardiovascular events, as are statins. NICE recommends using atorvastatin 80 mg with the aim of reducing non-HDL cholesterol concentration by at least 40%.³ The ESC aims to lower LDL-cholesterol concentration to below 1.8 mmol/L, or by at least 50% if this target cannot be reached. The routine administration of drugs to raise HDL-cholesterol or to lower triglyceride concentration is not recommended.

ACE inhibitors are recommended in patients with stable angina who have systolic left ventricular dysfunction

or diabetes, and by the ESC for patients with hypertension.

Risk stratification

NICE recommends that the possibility of left main stem and/or proximal 3-vessel disease, and the potential survival gain from coronary artery bypass grafting (CABG) with this anatomy, is discussed with patients whose symptoms are controlled following a diagnosis of CAD (web addendum table 3). It recommends that non-invasive functional or anatomical imaging is considered in order to identify patients who might benefit from CABG. The overlap between diagnostic testing and risk stratification means that, if NICE guidance is followed, some form of prognostic information will be available following a confirmed diagnosis of CAD for all patients except those who have typical angina and a PTP of CAD >90%.

Analogous to NICE, if the ESC diagnostic pathway is followed, only patients with a PTP of CAD >85% will not have diagnostic test results available for risk stratification, and the ESC recommends that these patients undergo stress imaging. The ESC defined an annual mortality rate >3% as high risk indicating the requirement for invasive coronary angiography, and it defined parameters for the exercise ECG, stress imaging (>10% ischaemic myocardium), and CT coronary angiography

Table 4 Summary of main recommendations regarding pharmacological management in patients with stable angina/stable coronary artery disease from NICE and the ESC

	NICE	ESC
Optimal medical therapy	Consists of one or two antianginal drugs as necessary, plus drugs for secondary prevention of cardiovascular disease	Indicates at least one drug for angina/ischaemia relief, plus drugs for event prevention. (I C)
Immediate symptom relief	Short-acting nitrate	Short-acting nitrate. (I B)
Angina prophylaxis:		
First line	β -Blocker and/or calcium channel blocker	β -Blocker and/or calcium channel blocker. (I A)
Second-line add-on therapy or alternative therapy when first-line agent contraindicated or not tolerated	Long-acting nitrate or ivabradine or nicorandil or ranolazine	Long-acting nitrate or ivabradine or nicorandil or ranolazine. (IIa B)
Asymptomatic patients with large areas of ischaemia (>10% myocardium)		Trimetazidine may be considered. (IIb B)
Event prevention	Aspirin 75 mg	β -Blockers should be considered. (IIa C)
	Statin in line with NICE clinical guideline on lipid modification*. Atorvastatin 80 mg to lower non-HDL-cholesterol by >40%	Low-dose aspirin. (I A)
	ACE inhibitor for patients with diabetes	Clopidogrel in cases of aspirin intolerance. (I B)
		Statin. (I A) Treatment target for LDL-cholesterol <1.8 mmol/L and/or >50% reduction
		ACE inhibitor (or ARB) if presence of other conditions (heart failure, hypertension, diabetes). (I A)

*This was NICE clinical guideline 67 when the NICE stable angina guideline was published. It recommended using Simvastatin 40 mg, increasing to Simvastatin 80 mg if blood concentrations of total cholesterol <4 mmol/L and LDL-cholesterol <2 mmol/L were not attained. An update to the lipid modification guidance, NICE clinical guideline 181, was published in July 2014 which recommended the use of Atorvastatin 80 mg with the aim of reducing the blood non-HDL cholesterol concentration by at least 40%.

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; ESC, European Society of Cardiology; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NICE, National Institute for Health and Care Excellence.

(left main stem disease, proximal 3-vessel disease, and proximal left anterior descending artery disease) which met this criterion. Where patients undergo invasive coronary angiography for symptomatic reasons, the ESC recommends that fractional flow reserve (FFR) may be required for risk stratification.

The ESC recommends that echocardiography is undertaken in all patients with suspected CAD, left ventricular impairment conferring an unfavourable prognosis.

Myocardial revascularisation

NICE recommends revascularisation (by CABG) for patients who have left main stem and/or proximal 3-vessel disease (web addendum table 4). By contrast, the ESC recommends revascularisation to improve prognosis in patients with left main stem disease $>50\%^*$, 2–3-vessel disease with impaired left ventricular function, proximal left anterior descending artery stenosis $>50\%^*$, single remaining vessel with $>50\%$ stenosis*, or a large area of ischaemia (*with documented ischaemia or FFR ≤ 0.8 for stenoses between 50% and 90%).

In symptomatic patients in whom either CABG or percutaneous coronary intervention (PCI) might be appropriate, NICE recommends that the risks and benefits of PCI and CABG are explained and, if no preference is expressed, that the evidence which suggests that PCI may be the more cost-effective procedure is taken into account in selecting treatment. In symptomatic patients with multivessel disease who have diabetes or are over 65 years, or who have anatomically complex 3-vessel disease with or without involvement of the left main stem, NICE recommends that the potential survival advantage of CABG is taken into account in selecting treatment. NICE hints at the use of the SYNTAX score in guiding treatment selection by recommending the use of a systematic approach to assess the severity and complexity of the patient's CAD while also considering their comorbidities. The ESC specifies the use of the SYNTAX score in determining the most appropriate mode of revascularisation in patients with left main stem and/or 3-vessel disease, and is more didactic than NICE in its recommendations regarding the mode of revascularisation in other patient groups. Specifically, it recommends CABG for patients with left main stem disease with 2-vessel or 3-vessel disease and a SYNTAX score ≥ 33 , and for patients with 3-vessel disease and a SYNTAX score ≥ 23 , and it recommends PCI for patients with 1-vessel or 2-vessel disease without proximal left anterior descending artery involvement, and for patients with left main stem with or without 1-vessel disease, ostium/mid-shaft disease, and patients at high surgical risk. In patients with diabetes with multivessel disease, the ESC favours CABG over PCI.

The multidisciplinary team meeting is promoted in both guidelines for clinical decision-making in more complex patients such as those with left main stem or

multivessel disease, complex coronary anatomy, or in patients with comorbidities.

DISCUSSION

The principle of formally assessing PTP of CAD and applying diagnostic testing in patients without a very low or very high PTP is applied in both guidelines. The main differences between the diagnostic algorithms are: (1) routine use of echocardiography by the ESC which determines the initial strategy in patients with typical angina and influences the choice of ischaemia testing in patients without typical angina when stress imaging is not available; (2) potential use of the exercise ECG by the ESC, but not by NICE; (3) stress imaging as first-choice diagnostic testing by the ESC in most patients who have a PTP 15–85% and (4) invasive coronary angiography as NICE's first diagnostic test in patients with a PTP of CAD $>60\%$.

The ESC's reliance on echocardiography was derived from the prognostic impact of left ventricular impairment observed in the Coronary Artery Surgery Study registry in which 12-year survival rates for patients with LVEF $\geq 50\%$, 35–49% and $<35\%$, were 73%, 54% and 21%, respectively.⁷ The $>3\%$ annual mortality rate in patients with LVEF $<50\%$ underlies the ESC's recommendation to undertake invasive coronary angiography in patients with typical angina and left ventricular impairment, and is predicated on the premise that revascularisation improves prognosis in this group of patients.

NICE concluded that the exercise ECG should not be used to diagnose CAD after considering the findings of a systematic review (147 studies; 24 074 patients) in which its weighted mean sensitivity and specificity in comparison with coronary angiography was 68% and 77%, respectively.⁸ The ESC determined from its literature review that the exercise ECG has a specificity of about 90% and a sensitivity of about 50%. The inferiority of the exercise ECG to stress imaging is acknowledged by the ESC, but it considers the exercise ECG valuable in low or intermediate-risk patients when there is no local access to stress imaging. Whether or not this relates to recognition that some parts of Europe do not have widespread availability of stress imaging is not clear, but ESC guidelines are intended for implementation across 56 countries which do not have equal healthcare resources. In the UK, at least one form of stress imaging is generally available, so the default, were these guidelines applied, would be for stress imaging in all patients with PTP 15–85% except for patients with both LVEF $<50\%$ and typical angina, who should undergo invasive coronary angiography.

The prevalence estimates for CAD used by NICE and the ESC are derived from two different studies.^{9 10} NICE includes the presence or absence of risk factors for CAD in its PTP table, whereas the ESC does not. The estimates of PTP used by NICE are very different in patients with and

without risk factors for CAD, particularly in younger patients, women, and men with atypical angina. The different PTP tables used in the two guidelines might contribute to the use of different diagnostic tests for similar patients.

Testing purely for risk stratification should be uncommon if the guidelines are followed, results being available from diagnostic testing in most patients. Because of the different diagnostic algorithms, risk stratification according to NICE guidelines is more often based on the results of invasive coronary angiography and, according to the ESC guidelines, is more often based on stress testing. Only patients with a high (>85–90%) PTP for CAD would not have diagnostic test results available, and these patients should undergo stress imaging according to the ESC, whereas NICE recommends that non-invasive functional or anatomical imaging is considered in order to identify patients who might benefit from CABG.

Both guidelines stress the importance of optimal medical therapy for patients with stable angina. Recommendations regarding pharmacological therapy are similar for most patients. NICE guidance to use simvastatin 40–80 mg daily for the secondary prevention of cardiovascular disease was superseded by guidance to use atorvastatin 80 mg daily in July 2014.³ This change was partly related to a reduction in atorvastatin acquisition costs which resulted in greater cost-effectiveness.

The most significant differences between NICE and ESC recommendations concern myocardial revascularisation. Greater emphasis on the use of the SYNTAX score to guide mode of revascularisation in patients with left main stem and/or 3-vessel disease in the ESC guideline is explained by the availability of the 3-year and 5-year follow-up data from the SYNTAX trial when the ESC drafted its guidance, data which were not available at the time of publication of the NICE guidance.^{11 12} In the SYNTAX trial, patients with left main stem and/or 3-vessel CAD were randomly allocated to CABG or PCI. Clinical outcomes were related to disease complexity measured by the SYNTAX score, the event-free survival curves diverging with time in favour of CABG in both anatomical groups in patients with a SYNTAX score ≥ 33 , and in patients with 3-vessel disease with a SYNTAX score ≥ 23 .

The more important differences, however, concern patients whose symptoms are well controlled on medical therapy. NICE recommends revascularisation (by CABG) to potentially improve prognosis only in patients with left main stem and/or proximal 3-vessel disease, whereas the ESC includes proximal left anterior descending artery disease among its indications for revascularisation to improve prognosis. The ESC also recommends that evidence of myocardial ischaemia is used to guide revascularisation decisions. By contrast, myocardial ischaemia is not seen as an indication for revascularisation by NICE, which recommends a randomised trial of interventional management versus continued drug treatment in people with stable angina and myocardial ischaemia on non-invasive functional testing, with all-cause

mortality and cardiovascular mortality as the primary endpoints. NICE also recommends that research is undertaken to clarify the clinical and cost-effectiveness of early revascularisation compared with continued drug treatment in patients with stable angina and multivessel disease (including left main stem disease) whose symptoms are controlled with optimal drug treatment.

These differences must be related to the respective guideline development group's interpretation of the available evidence. Two key questions are: (1) how important is it that the randomised trials which showed prognostic benefit from CABG predated widespread statin use? (2) do the observations that myocardial ischaemia is associated with an adverse prognosis, and that myocardial ischaemia can be reduced by myocardial revascularisation, justify myocardial revascularisation in the absence of significant symptoms? Certainly, the evidence to support 'ischaemia-guided' selection of stable patients for revascularisation is limited. In a recent meta-analysis of five randomised controlled trials which included 4064 patients with evidence of myocardial ischaemia, 5-year rates of death and non-fatal myocardial infarction (MI) were not significantly different between patients who were allocated to medical therapy plus PCI compared with medical therapy alone.¹³ Perhaps the results would have been different if FFR had been used to diagnose myocardial ischaemia? In FAME II, the only trial to randomise patients with a low FFR to PCI or no PCI, the rate of unplanned revascularisation was significantly reduced, but there was no reduction in death or MI in PCI-treated patients.¹⁴ It is a matter of opinion whether or not these data justify revascularisation in patients with ischaemia but with few symptoms.

TWO SETS OF GUIDELINES: IMPLICATIONS FOR PRACTICE

The NICE diagnostic guidelines changed clinical practice in the UK, most cardiologists moving away from the exercise ECG towards more accurate testing modalities for the diagnosis of CAD. The use of more sophisticated tests which, unlike the exercise ECG, cannot readily be undertaken at the initial assessment introduced logistical problems regarding their timely delivery. The ESC's diagnostic algorithm is based around stress imaging where facilities are available and the exercise ECG where stress imaging is not available.

The UK cardiologist moving to Europe would need to make few adjustments to his/her usual pharmacological management of patients with stable angina, though patients with hypertension would more often be treated with ACE inhibitors in Europe. It is probable that UK cardiologists will move towards the use of high-intensity statin therapy (specifically, atorvastatin 80 mg) in patients with stable angina following the 2014 update to NICE guidance on lipid modification, rather than reserving such therapy for patients after an ACS, and they will need to become familiar with a target based on

lowering non-HDL blood cholesterol concentration rather than LDL-cholesterol lowering.

The contrasting recommendations regarding revascularisation place UK cardiologists in a quandary; should they refer only patients with left main stem and/or proximal 3-vessel disease for revascularisation for prognostic reasons, as NICE recommends, or should they also refer patients with a lower burden of CAD if the proximal left anterior descending artery is affected, particularly if there is evidence of myocardial ischaemia? Clinical decision-making in multidisciplinary team meetings is heavily influenced by the consensus view on this point. Patients with stable angina who have disease involving the proximal left anterior descending artery are less likely to be referred for myocardial revascularisation if they are managed according to NICE guidance compared with ESC guidance.

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