European Heart Journal (2006) **27**, 1341–1381
doi:10.1093/eurheartj/ehl001

Guidelines on the management of stable angina pectoris: executive summary

The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology

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† CME questions for this article are available at *European Heart Journal* online.

Preamble

Guidelines and Expert Consensus Documents aim to present management recommendations based on all the relevant evidences on a particular subject in order to help physicians to select the best possible management strategies for the individual patient, suffering from a specific condition, not only taking into account the impact on outcome, but also the risk–benefit ratio of a particular diagnostic or therapeutic procedure. Numerous studies have demonstrated that patient outcomes improve when guideline recommendations, based on the rigorous assessment of evidence-based research, are applied in clinical practice.

A great number of Guidelines and Expert Consensus Documents have been issued in recent years by the European Society of Cardiology (ESC) and also by other organizations or related societies. The profusion of documents can put at stake the authority and credibility of guidelines, particularly if discrepancies appear between different documents on the same issue, as this can lead to confusion in the minds of physicians. To avoid these pitfalls, the ESC and other organizations have issued recommendations for formulating and issuing the Guidelines and Expert Consensus Documents. The ESC recommendations for guidelines production can be found on the ESC website (www.escardio.org). It is beyond the scope of this preamble to recall all but the basic rules.

In brief, the ESC appoints experts in the field to carry out a comprehensive review of the literature, with a view to making a critical evaluation of the use of diagnostic and therapeutic procedures and assessing the risk–benefit ratio of the therapies recommended for the management and/or prevention of a given condition. Estimates of expected health outcomes are included, where data exist. The strength of evidence for or against particular procedures or treatments is weighed, according to the pre-defined scales for grading recommendations and levels of evidence, as outlined subsequently.

The Task Force members of the writing panels, as well as the document reviewers, are asked to provide disclosure statements of all relationships they may have which might be perceived as real or potential conflicts of interest. These disclosure forms are kept on file at the European Heart House, Headquarters of the ESC and can be made available by written request to the ESC President. Any changes in conflict of interest that arise during the writing period must be notified to the ESC.

Guidelines and recommendations are presented in formats that are easy to interpret. They should help physicians to make clinical decisions in their daily routine by describing the range of generally acceptable approaches to diagnosis and treatment. However, the ultimate judgement regarding the care of an individual patient must be made by the physician in charge of his/her care.

The ESC Committee for Practice Guidelines (CPG) supervises and coordinates the preparation of new Guidelines and Expert Consensus Documents produced by the Task Forces, expert groups, or consensus panels. The committee is also responsible for the endorsement of these Guidelines and Expert Consensus Documents or statements.

Once the document has been finalized and approved by all the experts involved in the Task Force, it is submitted to outside specialists for review. In some cases, the document can be presented to a panel of key opinion leaders in Europe, specialists in the relevant condition at hand, for discussion and critical review. If necessary, the document is revised once more and finally approved by the CPG and selected members of the Board of the ESC and subsequently published.

After publication, dissemination of the message is of paramount importance. Publication of executive summaries and the production of pocket-sized and PDA-downloadable versions of the recommendations are helpful. However, surveys have shown that the intended end-users are often not aware of the existence of guidelines or simply don't put them into practice. Implementation programmes are thus necessary and form an important component of the dissemination of the knowledge. Meetings are organized by the ESC and directed towards its member National Societies and key opinion leaders in Europe. Implementation meetings can also be undertaken at a national level, once the guidelines have been endorsed by the ESC member societies and translated into the local language, when necessary.

Classes of recommendations

Class I	Evidence and/or general agreement that a given diagnostic procedure/treatment is beneficial, useful, and effective
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the treatment or procedure
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy
Class IIb	Usefulness/efficacy is less well established by evidence/opinion;
Class III	Evidence or general agreement that the treatment or procedure is not useful/effective and in some cases may be harmful

Altogether, the task of writing Guidelines or Expert Consensus Document covers not only the integration of the most recent research, but also the creation of educational

tools and the implementation programmes for the recommendations. The loop between clinical research, writing of guidelines, and implementing them into clinical practice can only be completed if surveys and registries are organized to verify that actual clinical practice is in keeping with what is recommended in the guidelines. Such surveys and registries also make it possible to check the impact of strict implementation of the guidelines on patient outcome.

Classes of recommendations

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries

Introduction

Stable angina pectoris is a common and sometimes disabling disorder. The development of new tools for the diagnostic and prognostic assessments of patients, along with the continually evolving evidence base for various treatment strategies, mandates that existing guidelines[1] be revised and updated. Therefore, the Task Force has obtained opinions from a wide variety of experts and has tried to achieve agreement on the best contemporary approaches to the care of stable angina pectoris, bearing in mind not only the efficacy and safety of treatments, but also the cost and the availability of resources. The Task Force has taken the view that these guidelines should reflect the pathophysiology and management of angina pectoris caused by myocardial ischaemia due to coronary artery disease (CAD), usually macrovascular but also microvascular in some of the patients. Furthermore, this Task Force does not deal with primary prevention, which has already been covered in other recently published guidelines[2] and has limited its discussion on secondary prevention. Recently published guidelines and consensus statements that overlap to a considerable extent with the remit of this document are listed in the complete version of the guidelines available on-line.

Definition and pathophysiology

Stable angina is a clinical syndrome characterized by discomfort in the chest, jaw, shoulder, back, or arms, typically elicited by exertion or emotional stress and relieved by rest or nitroglycerin. Less typically, discomfort may occur in the epigastric area. It is usual to confine the term to the cases in which the syndrome can be attributed to myocardial ischaemia, although essentially similar symptoms can be caused by disorders of the oesophagus, lungs, or chest wall. Although the most common cause of myocardial ischaemia is atherosclerotic CAD, demonstrable myocardial ischaemia may be induced by hypertrophic or dilated cardiomyopathy, aortic stenosis, or other rare cardiac conditions in the absence of obstructive atheromatous coronary disease, which are not considered in this document.

Epidemiology

The prevalence of angina increases sharply with age in both sexes from 0.1–1% in women aged 45–54 to 10–15% in women aged 65–74 and from 2–5% in men aged 45–54 to 10–20% in men aged 65–74. Therefore, it can be estimated that in most European countries, 20 000–40 000 individuals of the population per million suffer from angina.

Natural history and prognosis

Information on the prognosis associated with chronic stable angina is derived from long-term prospective population-based studies, clinical trials of anti-anginal therapy, and observational registries, with selection bias, an important factor to consider when evaluating and comparing the available data. Data from the Framingham Heart Study[3,4] showed that for men and women with an initial clinical presentation of stable angina, the 2-year incidence rates of non-fatal myocardial infarction and coronary heart disease (CHD) death were 14.3 and 5.5% in men and 6.2 and 3.8% in women, respectively. More contemporary data from the clinical trials of anti-anginal therapy and/or revascularization estimate the annual mortality rate to range from 0.9 to 1.4% per annum,[5–9] with an annual incidence of non-fatal MI between 0.5% (INVEST)[8] and 2.6% (TIBET).[6] These estimates are consistent with the observational registry data.[10]

However, within the population with stable angina, an individual's prognosis can vary considerably, up to 10-fold, depending on baseline clinical, functional, and anatomical factors, emphasizing the importance of careful risk stratification.

Diagnosis and assessment

Diagnosis and assessment of angina involve clinical assessment, laboratory tests, and specific cardiac investigations. Clinical assessment related to diagnosis and basic laboratory investigations are dealt with in this section. Cardiac specific investigations may be non-invasive or invasive and may be used to confirm the diagnosis of ischaemia in patients with suspected stable angina, to identify or exclude associated conditions or precipitating factors for risk stratification and to evaluate the efficacy of treatment. In practice, diagnostic and prognostic assessments are conducted in tandem rather than separately, and many of the investigations used for the diagnosis also offer prognostic information. For the purposes of description and presentation of the evidence, the individual investigative techniques are discussed subsequently with recommendations for diagnosis. Specific cardiac investigations routinely used for risk stratification purposes are discussed separately in the subsequent section. An algorithm for the initial evaluation of patients presenting with clinical symptoms suggestive of angina is depicted in *Figure 1*.

Symptoms and signs

A careful history remains the cornerstone of the diagnosis of angina pectoris. In the majority of cases, it is possible to make a confident diagnosis on the basis of the history alone, although physical examination and objective tests are necessary to confirm the diagnosis and assess the severity of underlying disease.

The characteristics of discomfort related to myocardial ischaemia (angina pectoris) have been extensively described

and may be divided into four categories: location, character, duration and relation to exertion, and other exacerbating or relieving factors. The discomfort caused by myocardial ischaemia is usually located in the chest, near the sternum, but may be felt anywhere from the epigastrium to the lower jaw or teeth, between the shoulder blades or in either arm to the wrist and fingers. The discomfort is usually described as pressure, tightness, or heaviness, sometimes strangling, constricting, or burning. The severity of the discomfort varies greatly and is not related to the severity of the underlying coronary disease. Shortness of breath may accompany angina, and chest discomfort may also be accompanied by less specific symptoms such as fatigue or faintness, nausea, burping, restlessness, or a sense of impending doom.

The duration of the discomfort is brief, not more than 10 min in the majority of cases, and more commonly even less. An important characteristic is the relation to exercise, specific activities, or emotional stress. Symptoms classically deteriorate with increased levels of exertion, such as walking up an incline or against a breeze, and rapidly disappear within a few minutes, when these causal factors abate. Exacerbations of symptoms after a heavy meal or first thing in the morning are classical features of angina. Buccal or sublingual nitrates rapidly relieve angina, and a similar

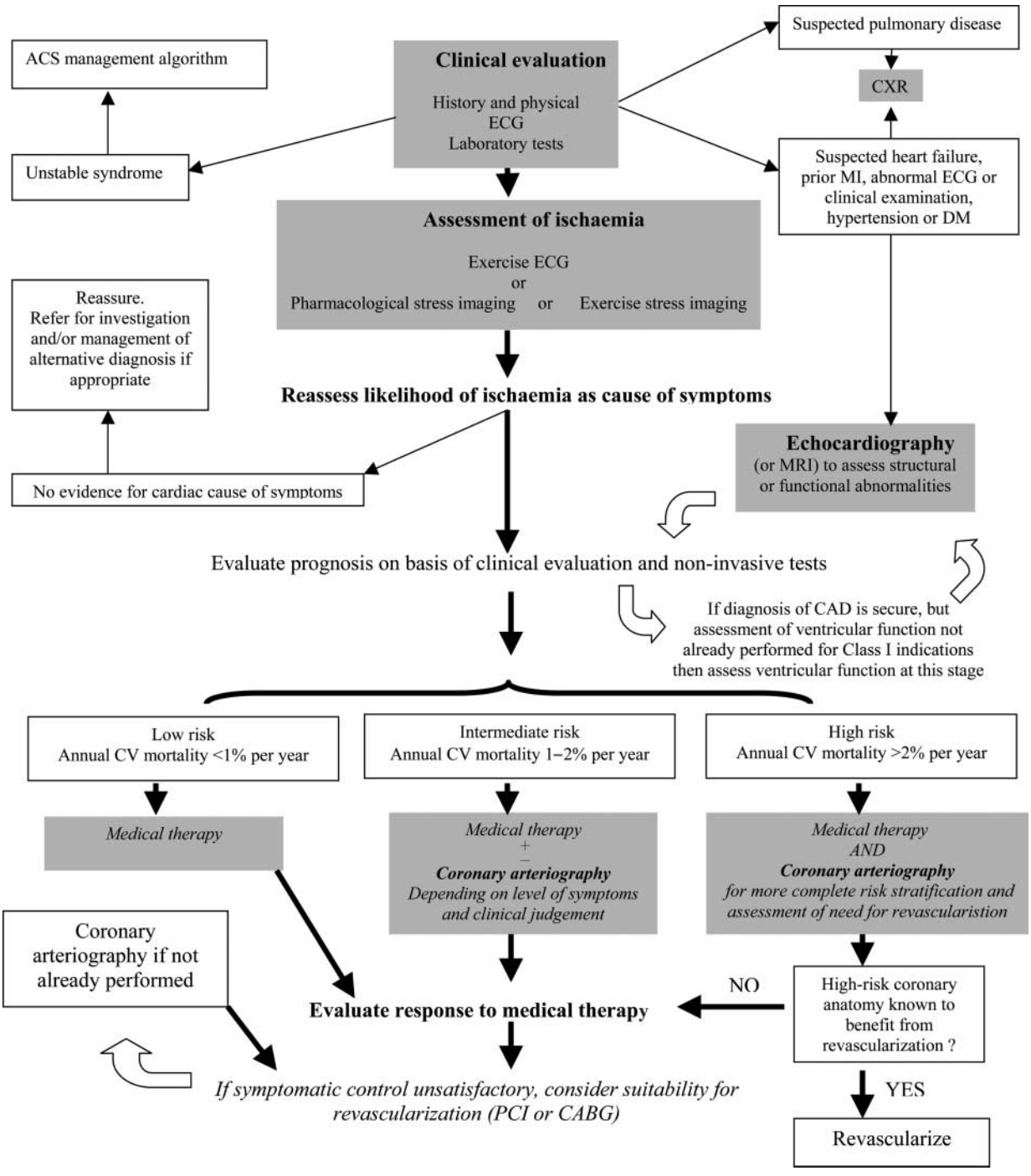

Figure 1 Algorithm for the initial evaluation of patients with clinical symptoms of angina.

rapid response may be observed with chewing nifedipine capsules.

Non-anginal pain lacks the characteristic qualities described, may involve only a small portion of the left hemithorax, and last for several hours or even days. It is usually not relieved by nitroglycerin (although it may be in the case of oesophageal spasm) and may be provoked by palpation. Non-cardiac causes of pain should be evaluated in such cases.

Definitions of typical and atypical angina have been previously published[11] and are summarized in *Table 1*. It is important when taking the history to identify those patients with unstable angina, which may be associated with plaque rupture, who are at significantly higher risk of an acute coronary event in the short-term. Unstable angina may present in one of three ways: (i) as rest angina, i.e. pain of characteristic nature and location, but occurring at rest and for prolonged periods, up to 20 min; (ii) rapidly increasing or crescendo angina, i.e. previously stable angina, which progressively increases in severity, intensity, and at lower threshold over a short period of 4 weeks or less; or (iii) new onset angina, i.e. recent onset of severe angina, such that the patient experiences marked limitation of ordinary activity within 2 months of initial presentation. The investigation and management of suspected unstable angina are dealt with in guidelines for the management of acute coronary syndromes.

For patients with stable angina, it is also useful to classify the severity of symptoms using a grading system such as that of the Canadian Cardiovascular Society Classification (*Table 2*).[12] Alternative classification systems such as the Duke Specific Activity Index[13] and the Seattle angina questionnaire[14] may also be used in determining the functional impairment of the patient and quantifying response to therapy and may offer superior prognostic capability.[15]

Physical examination of a patient with (suspected) angina pectoris is important to assess the presence of hypertension, valvular heart disease, or hypertrophic obstructive cardiomyopathy. Physical examination should include the assessment of body mass index (BMI) and waist circumference to assist evaluation of the metabolic syndrome,[16,17] evidence of non-coronary vascular disease which may be asymptomatic, and other signs of comorbid conditions. During or immediately after an episode of myocardial ischaemia, a third or fourth heart beat may be heard and mitral insufficiency may also be apparent during ischaemia. However, such signs are elusive and non-specific.

Table 1 Clinical classification of chest pain

Typical angina (definite)	Meets three of the following characteristics Substernal chest discomfort of characteristic quality and duration Provoked by exertion or emotional stress Relieved by rest and/or GTN
Atypical angina (probable)	Meets two of the above characteristics
Non-cardiac chest pain	Meets one or none of the above characteristics

Laboratory tests

Laboratory investigations may be loosely grouped into those that provide information related to possible causes of ischaemia, those that may be used to establish cardiovascular risk factors and associated conditions, and those that may be used to determine prognosis.

Haemoglobin and, where there is a clinical suspicion of a thyroid disorder, thyroid hormones provide information related to possible causes of ischaemia. The full blood count incorporating total white cell count as well as haemoglobin may also add prognostic information.[18] Serum creatinine is a simple if crude method to evaluate renal function and is recommended at initial evaluation in all patients with suspected angina. If there is a clinical suspicion of instability, biochemical markers of myocardial damage such as troponin or creatinine kinase myocardial band (measured by the mass assay) should be employed to exclude myocardial injury. If these markers are elevated, management should continue as for an acute coronary syndrome rather than stable angina. After initial assessment, these tests are not recommended as routine investigations during each subsequent evaluation.

Fasting plasma glucose and fasting lipid profile including total cholesterol (TC), high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol, and triglycerides should be evaluated in all patients with suspected ischaemic disease, including stable angina, to establish the patient's risk profile and ascertain the need for treatment. Lipid profile and glycaemic status should be re-assessed periodically to determine efficacy of treatment, and in non-diabetic patients, to detect new development of diabetes. There is no evidence to support recommendations for how regularly re-assessment should take place. Consensus suggests annual measurement. Patients with very high levels of lipids or glucose, in whom the progress of any intervention needs to be monitored, should have measurements more frequently.

Elevations of fasting or post-glucose challenge glycaemia and HbA1c have also been shown to predict adverse outcome independently of conventional risk factors. Obesity and, in particular, evidence of the metabolic syndrome are predictive of adverse cardiovascular outcome in patients with established disease as well as in asymptomatic populations. The presence of the metabolic syndrome can be determined from the assessment of waist circumference (or BMI), blood pressure, HDL, and triglycerides and fasting glucose levels and offers

Table 2 Classification of angina severity according to the Canadian Cardiovascular Society

Class	Level of symptoms
Class I	'Ordinary activity does not cause angina' Angina with strenuous or rapid or prolonged exertion only
Class II	'Slight limitation of ordinary activity' Angina on walking or climbing stairs rapidly, walking uphill or exertion after meals, in cold weather, when under emotional stress, or only during the first few hours after awakening
Class III	'Marked limitation of ordinary physical activity' Angina on walking one or two blocks on the level or one flight of stairs at a normal pace under normal conditions[a]
Class IV	'Inability to carry out any physical activity without discomfort' or 'angina at rest'

[a]Equivalent to 100–200 m.

additional prognostic information to that obtained from the conventional Framingham risk scores[19] without major additional cost in terms of laboratory investigation.

Further laboratory testing, including cholesterol subfractions (ApoA and ApoB) homocysteine, lipoprotein (a) (Lpa), haemostatic abnormalities[20] and markers of inflammation such as hs C-reactive protein,[21] has been the subject of much interest as methods to improve current risk prediction.[21,22] However, markers of inflammation fluctuate over time and may not be a reliable estimator of risk in the long-term.[23] More recently, NT-BNP has been shown to be an important predictor of long-term mortality independent of age ventricular ejection fraction (EF) and conventional risk factors.[24] As yet, there is no adequate information regarding how modification of these biochemical indices can significantly improve on current treatment strategies to recommend their use in all patients, particularly given the constraints of cost and availability. Nevertheless, these measurements have a role in selected patients, for example, testing for haemostatic abnormalities in those with prior MI without conventional risk factors,[25] or a strong family history of coronary disease, or where resources are not limited. Further research regarding their use is welcome.

Recommendations for laboratory investigation in initial assessment of angina
Class I (in all patients)

(1) Fasting lipid profile, including TC, LDL, HDL, and triglycerides (level of evidence B)
(2) Fasting glucose (level of evidence B)
(3) Full blood count including Hb and WCC (level of evidence B)
(4) Creatinine (level of evidence C)

Class I (if specifically indicated based on clinical evaluation)

(1) Markers of myocardial damage if evaluation suggests clinical instability or acute coronary syndrome (level of evidence A)
(2) Thyroid function if clinically indicated (level of evidence C)

Class IIa

(1) Oral glucose tolerance test (level of evidence B)

Class IIb

(1) Hs C-reactive protein (level of evidence B)
(2) Lipoprotein a, ApoA, and ApoB (level of evidence B)
(3) Homocysteine (level of evidence B)
(4) HbA1c (level of evidence B)
(5) NT-BNP (level of evidence B)

Recommendations for blood tests for routine re-assessment in patients with chronic stable angina
Class IIa

(1) Fasting lipid profile and fasting glucose on an annual basis (level of evidence C)

Chest X-ray
A chest X-ray (CXR) is frequently used in the assessment of patients with suspected heart disease. However, in stable angina, the CXR does not provide specific information for diagnosis or for risk stratification. The test should be requested only in patients with suspected heart failure, valvular disease, or pulmonary disease. The presence of cardiomegaly, pulmonary congestion, atrial enlargement, and cardiac calcifications have been related to prognosis.

Recommendations for CXR for initial diagnostic assessment of angina
Class I

(1) CXR in patients with suspected heart failure (level of evidence C)
(2) CXR in patients with clinical evidence of significant pulmonary disease (level of evidence B)

Non-invasive cardiac investigations

This section will describe investigations used in the assessment of angina and concentrate on recommendations for their use in diagnosis and evaluation of efficacy of treatment, whereas recommendations for risk stratification will be dealt in the following section. As there are few randomized trials assessing health outcomes for diagnostic tests, the available evidence has been ranked according to the evidence from non-randomized studies or meta-analyses of these studies.

Resting ECG
All patients with suspected angina pectoris based on symptoms should have a resting 12-lead electrocardiogram (ECG) recorded. It should be emphasized that a normal resting ECG is not uncommon even in patients with severe angina and does not exclude the diagnosis of ischaemia. However, the resting ECG may show signs of CAD such as previous myocardial infarction or an abnormal repolarization pattern. The ECG may assist in clarifying the differential diagnosis if taken in the presence of pain, allowing detection of dynamic ST-segment changes in the presence of ischaemia, or by identifying features of pericardial disease. An ECG during pain may be particularly useful if vasospasm is suspected. The ECG may also show other abnormalities such as left ventricular hypertrophy (LVH), bundle branch block, pre-excitation, arrhythmias, or conduction defects. Such information may be helpful in defining the mechanisms responsible for chest pain, in selecting appropriate further investigation or in tailoring individual patient treatment. The resting ECG also has an important role in risk stratification, as outlined in the section on risk stratification.There is little direct evidence to support routinely repeating the resting ECG at frequent intervals, unless to obtain an ECG during pain or if there has been a change in functional class.

Recommendations for resting ECG for initial diagnostic assessment of angina
Class I (in all patients)

(1) Resting ECG while pain free (level of evidence C)
(2) Resting ECG during episode of pain (if possible) (level of evidence B)

Recommendations for resting ECG for routine re-assessment in patients with chronic stable angina
Class IIb

(1) Routine periodic ECG in the absence of clinical change (level of evidence C)

ECG stress testing

Exercise ECG is more sensitive and specific than the resting ECG for detecting myocardial ischaemia and for reasons of availability, and cost is the test of choice to identify inducible ischaemia in the majority of patients with suspected stable angina. There are numerous reports and meta-analyses of the performance of exercise ECG for the diagnosis of coronary disease.[26–29] Using exercise ST-depression to define a positive test, the reported sensitivity and specificity for the detection of significant coronary disease range between 23 and 100% (mean 68%) and 17 and 100% (mean 77%), respectively. The majority of reports are of studies where the population tested did not have significant ECG abnormalities at baseline and were not on anti-anginal therapy or were withdrawn from anti-anginal therapy for the purposes of the test. Exercise ECG testing is not of diagnostic value in the presence of left bundle branch block (LBBB), paced rhythm, and Wolff Parkinson White (WPW) syndrome in which cases the ECG changes cannot be evaluated. Additionally, false positive results are more frequent in patients with abnormal resting ECG in the presence of LVH, electrolyte imbalance, intraventricular conduction abnormalities, and use of digitalis. Exercise ECG testing is also less sensitive and specific in women.[30]

Interpretation of exercise ECG findings requires a Bayesian approach to diagnosis. This approach uses clinicians' pre-test estimates of disease along with the results of diagnostic tests to generate individualized post-test disease probabilities for a given patient. The pre-test probability is influenced by the prevalence of the disease in the population studied, as well as clinical features in an individual.[31] Therefore, for the detection of coronary disease, the pre-test probability is influenced by age and gender, and further modified by the nature of symptoms at an individual patient level before the results of exercise testing are used to determine the posterior or post-test probability.

In assessing the significance of the test, not only the ECG changes but also the workload, heart rate increase and blood pressure response, heart rate recovery after exercise, and the clinical context should be considered.[32] It has been suggested that evaluating ST-changes in relation to heart rate improves the reliability of diagnosis,[33] but this may not be so in symptomatic populations.[34]

An exercise test should be carried out only after careful clinical evaluation of symptoms and a physical examination including resting ECG. Exercise ECG should not be carried out routinely in patients with known severe aortic stenosis or hypertrophic cardiomyopathy, although carefully supervised exercise testing may be used to assess functional capacity in selected individuals with these conditions.

The reason for stopping the test and the symptoms at that time, including their severity, should be recorded. Time to onset of ECG changes and/or symptoms, the overall exercise time, the blood pressure and heart rate response, the extent and severity of ECG changes, the post-exercise recovery rate of ECG changes, and heart rate should also be assessed. For repeated exercise tests, the use of the Borg scale or similar method of quantifying symptoms may be used to allow comparisons.[35] Reasons to terminate an exercise test are listed in *Table 3*.

In some patients, the exercise ECG may be non-conclusive, for example, if at least 85% of maximum heart rate is not achieved in the absence of symptoms or ischaemia, if exercise is limited by orthopaedic or other non-cardiac problems, or ECG changes are equivocal. Unless the patient has a very low pre-test probability (<10% probability) of disease, an inconclusive exercise test should be followed by an alternative non-invasive diagnostic test. Furthermore, a 'normal' test in patients taking anti-ischaemic drugs does not rule out significant coronary disease.[36] For diagnostic purposes, the test should be conducted in patients not taking anti-ischaemic drugs, although this may not always be possible or considered safe.

Exercise stress testing can also be useful to evaluate the efficacy of treatment after control of angina with medical treatment or revascularization or to assist prescription of exercise after control of symptoms, but the effect of routine periodical exercise testing on patient outcomes has not been formally evaluated.

Table 3 Reasons to terminate the exercise stress test

The exercise stress test is terminated for one of the following reasons:

1. Symptom limitation, e.g. pain, fatigue, dyspnoea, and claudication;
2. Combination of symptoms such as pain with significant ST-changes;
3. Safety reasons such as
   a. Marked ST-depression (>2 mm ST-depression can be taken as a relative indication for termination and ≥4 mm as an absolute indication to stop the test),
   b. ST-elevation ≥1 mm,
   c. Significant arrhythmia,
   d. Sustained fall in systolic blood pressure >10 mmHg,
   e. Marked hypertension (>250 mmHg systolic or >115 mmHg diastolic);
4. Achievement of maximum predicted heart rate may also be a reason to terminate the test in patients with excellent exercise tolerance who are not tired and at the discretion of the supervising physician.

Recommendations for exercise ECG for initial diagnostic assessment of angina

Class I

(1) Patients with symptoms of angina and intermediate-to-high pre-test probability of coronary disease based on age, gender, and symptoms, unless unable to exercise or displays ECG changes which make ECG non-evaluable (level of evidence B)

Class IIb

(1) Patients with ≥1 mm ST-depression on resting ECG or taking digoxin (level of evidence B)
(2) Patients with low pre-test probability (<10%) of coronary disease based on age, gender, and symptoms (level of evidence B)

Recommendations for exercise ECG for routine re-assessment in patients with chronic stable angina

Class IIb

(1) Routine periodic exercise ECG in the absence of clinical change (level of evidence C)

Stress testing in combination with imaging

The most well-established stress imaging techniques are echocardiography and perfusion scintigraphy. Both may be used in combination with either exercise stress or pharmacological stress, and many studies have been conducted evaluating their use in both prognostic and diagnostic assessments. Novel stress imaging techniques also include stress MRI, which, for logistical reasons, is most frequently performed using pharmacological stress rather than exercise stress.

Stress imaging techniques have several advantages over the conventional exercise ECG testing including superior diagnostic performance (*Table 4*) for the detection of obstructive coronary disease, the ability to quantify and localize areas of ischaemia, the ability to provide diagnostic information in the presence of resting ECG abnormalities, or inability of the patient to exercise. Stress imaging techniques are often preferred in patients with previous percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) because of superior ability to localize ischaemia. In patients with angiographically confirmed intermediate coronary lesions, evidence of anatomically appropriate ischaemia is predictive of future events, whereas a negative stress imaging test can be used to define patients with a low cardiac risk, who can be re-assured.

Exercise testing with echocardiography. Exercise stress echocardiography has been developed as an alternative to 'classical' exercise testing with ECG and as an additional investigation to establish the presence or location and extent of myocardial ischaemia during stress. A resting echocardiogram is acquired before a symptom-limited exercise test is performed, most frequently using a bicycle ergometer, with further images acquired where possible during each stage of exercise and at peak exercise. This may be technically challenging.[37] Reported sensitivities and specificities for the detection of significant coronary disease range from 53 to 93% and from 70 to 100%, respectively. Depending on the meta-analysis, pooled sensitivity and specificity of exercise echocardiography are reported as 80–85% and 84–86%, respectively.[38–41] Recent improvements in technology include improvements in endocardial border definition with the use of contrast agents to facilitate identification of regional wall motion abnormalities and the use of injectable agents to image myocardial perfusion.[42]

Table 4 Summary of test characteristics for investigations used in the diagnosis of stable angina

	Diagnosis of CAD	
	Sensitivity (%)	Specificity (%)
Exercise ECG	68	77
Exercise echo	80–85	84–86
Exercise myocardial perfusion	85–90	70–75
Dobutamine stress echo	40–100	62–100
Vasodilator stress echo	56–92	87–100
Vasodilator stress myocardial perfusion	83–94	64–90

Advances in tissue Doppler and strain rate imaging are even more promising.

Tissue Doppler imaging allows regional quantification of myocardial motion (velocity), and strain and strain rate imaging allow determination of regional deformation, strain being the difference in velocities between adjacent regions and strain rate being the difference per unit length. Tissue Doppler imaging and strain rate imaging have improved the diagnostic performance of stress echocardiography,[43] thus improving the capability of echocardiography to detect ischaemia earlier in the ischaemic cascade. Because of the quantitative nature of the techniques, inter-operator variability and subjectivity in interpretation of the results are also reduced. Hence, tissue Doppler and strain rate imaging are expected to complement current echocardiographic techniques for ischaemia detection and improve the accuracy and reproducibility of stress echocardiography in the broader clinical setting. There is also some evidence that tissue Doppler imaging may improve the prognostic utility of stress echocardiography.[44]

Exercise testing with myocardial perfusion scintigraphy. Thallium-201 and technetium-99m radiopharmaceuticals are the most commonly used tracers, employed with single-photon emission computed tomography (SPECT) in association with a symptom-limited exercise test on either a bicycle ergometer or a treadmill. Although multiple-view planar images were first employed for myocardial perfusion scintigraphy, they have been largely replaced by SPECT, which is superior from the standpoint of localization, quantification, and image quality. SPECT perfusion scintigraphy is performed to produce images of regional tracer uptake that reflects relative regional myocardial blood flow. With this technique, myocardial hypoperfusion is characterized by reduced tracer uptake during stress in comparison with uptake at rest. Increased uptake of myocardial perfusion agent in the lung fields identifies patients with severe and extensive CAD. SPECT perfusion provides a more sensitive and specific prediction of the presence of CAD than exercise electrocardiography. Without correction for referral bias, the reported sensitivity of exercise scintigraphy has generally ranged from 70 to 98% and specificity from 40 to 90%, with mean values in the range of 85–90% and 70–75%, depending on the meta-analysis.[40,41,45,46]

Pharmacological stress testing with imaging techniques. Although the use of exercise imaging is preferable where possible, as it allows for more physiological reproduction of ischaemia and assessment of symptoms, pharmacological stress may also be employed. Pharmacological stress testing with either perfusion scintigraphy or echocardiography is indicated in patients who are unable to exercise adequately or may be used as an alternative to exercise stress. Two approaches may be used to achieve this: (i) infusion of short-acting sympathomimetic drugs such as dobutamine in an incremental dose protocol which increases myocardial oxygen consumption and mimics the effect of physical exercise or (ii) infusion of coronary vasodilators (e.g. adenosine and dipyridamole), which provide a contrast between regions supplied by non-diseased coronary arteries where perfusion increases and regions supplied by haemodynamically significant stenotic coronary arteries where perfusion will increase less or even decrease (steal phenomenon).

In general, pharmacological stress is safe and well tolerated by patients. Particular care must be taken to ensure that patients receiving vasodilators (adenosine or dipyridamole) are not already receiving dipyridamole for antiplatelet or other purposes and that caffeine is avoided in the 12–24 h preceding the study, as it interferes with their metabolism. Adenosine may precipitate bronchospasm in asthmatic individuals, but in such cases, dobutamine may be used as an alternative stressor. The diagnostic performance of pharmacological stress perfusion and pharmacological stress echo is also similar to that of exercise imaging techniques. Reported sensitivity and specificity for dobutamine stress echo and for vasodilator stress range from 40 to 100% and 62 to 100% and from 56 to 92% and 87 to 100%, respectively.[39,40] Sensitivity and specificity for the detection of coronary disease with adenosine SPECT range from 83 to 94% and 64 to 90%.[40]

On the whole, stress echo and stress perfusion scintigraphy, whether using exercise or pharmacological stress, have very similar applications. The choice as to which is employed depends largely on local facilities and expertise. Advantages of stress echocardiography over stress perfusion scintigraphy include a higher specificity, the possibility of a more extensive evaluation of the cardiac anatomy and function, and greater availability and lower cost, in addition to being free of radiation. However, at least 5–10% of patients have an inadequate echo window. The development of quantitative echocardiographic techniques such as tissue Doppler imaging is a step towards increasing the interobserver agreement and reliability of stress echo.

Although there is evidence to support superiority of stress imaging techniques over exercise ECG in terms of diagnostic performance, the costs of using a stress imaging test as first line investigation in all comers are considerable. However, stress imaging has an important role to play in evaluating patients with a low pre-test probability of disease, particularly women,[47,48] when exercise testing is inconclusive, in selecting lesions for revascularization and in assessing ischaemia after revascularization.[49,50]

A description of the methods of detection of myocardial viability is beyond the scope of these guidelines, but a report on the imaging techniques for the detection of hibernating myocardium has been previously published by an ESC working group.[51] Finally, although stress imaging techniques may allow for accurate evaluation of changes in the localization and extent of ischaemia over time and in response to treatment, periodic stress imaging in the absence of any change in clinical status is not recommended as routine.

Recommendations for the use of exercise stress with imaging techniques (either echocardiography or perfusion) in the initial diagnostic assessment of angina

Class I

(1) Patients with resting ECG abnormalities, LBBB, >1 mm ST-depression, paced rhythm, or WPW which prevent accurate interpretation of ECG changes during stress (level of evidence B)
(2) Patients with a non-conclusive exercise ECG but reasonable exercise tolerance, who do not have a high probability of significant coronary disease and in whom the diagnosis is still in doubt (level of evidence B)

Class IIa

(1) Patients with prior revascularization (PCI or CABG) in whom localization of ischaemia is important (level of evidence B)
(2) As an alternative to exercise ECG in patients where facilities, costs, and personnel resources allow (level of evidence B)
(3) As an alternative to exercise ECG in patients with a low pre-test probability of disease such as women with atypical chest pain (level of evidence B)
(4) To assess functional severity of intermediate lesions on coronary arteriography (level of evidence C)
(5) To localize ischaemia when planning revascularization options in patients who have already had arteriography (level of evidence B)

Recommendations for the use of pharmacological stress with imaging techniques (either echocardiography or perfusion) in the initial diagnostic assessment of angina

Class I, IIa, and IIb indications as mentioned earlier, if the patient is unable to exercise adequately.

Stress cardiac magnetic resonance. Cardiac magnetic resonance (CMR) stress testing in conjunction with a dobutamine infusion can be used to detect wall motion abnormalities induced by ischaemia or perfusion abmormalities. Detection of wall motion abnormalities has been shown to compare favourably to dobutamine stress echocardiography due to higher quality imaging.[52] Although CMR perfusion is still in development for clinical application, the results are already very good in comparison with X-ray coronary angiography, positron emission tomography, and SPECT.

A recent consensus panel reviewing the current indications for CMR thus gave class II recommendations for CMR wall motion and CMR perfusion imaging (class II provides clinically relevant information and is frequently useful; other techniques may provide similar information; supported by limited literature).[53]

Echocardiography at rest

Resting two-dimensional and doppler echocardiography is useful to detect or rule out the possibility of other disorders such as valvular heart disease[54] or hypertrophic cardiomyopathy[55] as a cause of symptoms and to evaluate ventricular function.[38] For purely diagnostic purposes, echo is useful in patients with clinically detected murmurs, history and ECG changes compatible with hypertrophic cardiomyopathy or previous myocardial infarction and symptoms or signs of heart failure. Cardiac magnetic resonance may be also be used to define structural cardiac abnormalities and to evaluate ventricular function, but routine use for such purposes is limited by availability.

Recent developments in tissue Doppler imaging and strain rate measurement have greatly improved the ability to study diastolic function,[56,57] but the clinical implications of isolated diastolic dysfunction in terms of treatment or prognosis are less well defined. Although the diagnostic yield of the evaluation of cardiac structure and function in patients with angina is mostly concentrated in specific subgroups, the estimation of ventricular function is extremely important in risk stratification, where echocardiography (or alternative methods of assessment of ventricular function) has much wider indications.

Recommendations for echocardiography for initial diagnostic assessment of angina
Class I

(1) Patients with abnormal auscultation suggesting valvular heart disease or hypertrophic cardiomyopathy (level of evidence B);
(2) Patients with suspected heart failure (level of evidence B)
(3) Patients with prior MI (level of evidence B)
(4) Patients with LBBB, Q waves or other significant pathological changes on ECG, including electrocardiographic left anterior hemiblock (LVH) (level of evidence C)

Ambulatory ECG monitoring. Ambulatory electrocardiographic (Holter) monitoring may reveal evidence of myocardial ischaemia during normal 'daily' activities[58] but rarely adds important diagnostic or prognostic information in chronic stable angina pectoris over and above that provided by an exercise test.[59,60] Ambulatory monitoring may have a role, however, in patients in whom vasospastic angina is suspected. Finally, in patients with stable angina and suspected major arrhythmias, holter monitoring is an important method of diagnosing arrhythmias. Repeated ambulatory ECG monitoring as means to evaluate patients with chronic stable angina is not recommended.

Recommendations for ambulatory ECG for initial diagnostic assessment of angina
Class I

(1) Angina with suspected arrhythmia (level of evidence B)

Class IIa

(1) Suspected vasospastic angina (level of evidence C)

Non-invasive techniques to assess coronary calcification and coronary anatomy
Computed tomography. Electron beam computed tomography (EBCT) and multi-detector or multi-slice CT (HDCT) have been validated as effective in detection or coronary calcium and quantification of the extent of coronary calcification. The Agatston score,[61] the most commonly used score, is based on the area and density of calcified plaques. It is computed by specific software and is used to quantify the extent of coronary calcification. In population based studies detection of coronary calcium may identify those at higher risk of significant coronary disease, but assessment of coronary calcification is not recommended routinely for the diagnostic evaluation of patients with stable angina.[62,63]

Image acquisition times and resolution for EBCT and MDCT have been shortened to the extent that CT coronary arteriography can be performed by injection of intravenous contrast agents.[64] MDCT or Multislice CT appears the most promising of the two techniques in terms of non-invasive imaging of the coronary arteries, with preliminary studies suggesting excellent definition, and the possibility of examining arterial wall and plaque characteristics. Sensitivity and specificity (segment specific) of CT angiography for the detection of coronary disease have been reported to be 95 and 98%, respectively, using 16 slice CT scanners.[65] Studies using 64 detector scanning report sensitivities and specificities of 90–94% and 95–97%, respectively, and importantly, a negative predictive value of 93–99%.[66,67] A conservative suggestion for CT angiography would be in patients with a low pre-test (<10%) probability of disease with an equivocal functional test (exercise ECG or stress imaging).

Recommendations for the use of CT angiography in stable angina
Class IIb

(1) Patients with a low pre-test probability of disease, with a non-conclusive exercise ECG or stress imaging test (level of evidence C)

Magnetic resonance arteriography. Similarly to the case of CT, advances in magnetic resonance technology permit non-invasive MR contrast coronary arteriography.[53] However, at present this can only be regarded as a valuable tool for research and is not recommended as routine clinical practice in the diagnostic evaluation of stable angina.

Invasive techniques to assess coronary anatomy

Coronary arteriography
Coronary arteriography is generally undertaken as part of a series of tests to establish a diagnosis and ascertain treatment options. Non-invasive testing can establish the likelihood of the presence of obstructive coronary disease with an acceptable degree of certainty, and through appropriate risk stratification may be used to determine the need for coronary arteriography for further risk stratification purposes. However, it may be contraindicated for reasons of disability or serious comorbidity or offer inconclusive results. After a resuscitated cardiac arrest or life threatening ventricular arrhythmia, a definitive diagnosis regarding the presence or absence of coronary disease is useful in clinical decision making.[68,69] Additionally, non-invasive testing does not allow assessment of suitability for revascularization, which may be considered for symptomatic as well as prognostic grounds. Coronary arteriography holds a fundamental position in the investigation of patients with stable angina, providing reliable anatomical information to identify the presence or absence of coronary lumen stenosis, define therapeutic options (suitability of medical treatment or myocardial revascularization) and determine prognosis. The composite rate of major complications associated with routine diagnostic catheterization in patients is 1–2%. The composite rate of death, MI, or stroke of the order of 0.1–0.2%.[70]

Conventional coronary arteriography identifies the extent of luminal obstruction, but other invasive techniques, such as intravascular ultrasound (IVUS) or intracoronary physiological measurements, allow more complete assessment of intracoronary lesions. IVUS, or measurement of coronary flow velocity (coronary vasodilatory reserve), or intracoronary artery pressure (fractional flow reserve) may be particularly useful in assisting management of patients with lesions of intermediate severity on arteriography or to facilitate optimal percutaneous intervention, but are not routinely required in the investigation of stable angina (see full text document on www.escardio.org).

Recommendations for coronary arteriography for the purposes of establishing a diagnosis in stable angina
Class I

(1) Severe stable angina (Class 3 or greater of Canadian Cardiovascular Society Classification), with a high

pre-test probability of disease, particularly if the symptoms are inadequately responding to medical treatment. (level of evidence B)
(2) Survivors of cardiac arrest (level of evidence B)
(3) Patients with serious ventricular arrhythmias (level of evidence C)
(4) Patients previously treated by myocardial revascularization (PCI, CABG), who develop early recurrence of moderate or severe angina pectoris (level of evidence C)

Class IIa

(1) Patients with an inconclusive diagnosis on non-invasive testing or conflicting results from different non-invasive modalities at intermediate to high risk of coronary disease (level of evidence C)
(2) Patients with a high risk of restenosis after PCI, if PCI has been performed in a prognostically important site (level of evidence C)

Risk stratification

The long-term prognosis of stable angina is variable, and the range of treatment options has expanded considerably from simple symptomatic control to potent and often expensive strategies to improve prognosis. When discussing risk stratification in stable angina, risk refers primarily to the risk of cardiovascular death, but the term is often more loosely applied to incorporate cardiovascular death and myocardial infarction, or in some cases even wider combinations of cardiovascular endpoints. The process of risk stratification serves a dual purpose, to facilitate an informed response to queries regarding prognosis from patients themselves, employers, insurers, non-cardiology specialists considering treatment options for comorbid conditions and others and secondly to assist in choosing appropriate treatment.

For certain management options, particularly revascularization and/or intensified pharmacological therapy, prognostic benefit is only apparent in high risk subgroups, with limited if any benefit in those whose prognosis is already good. This mandates identification of those patients at highest risk, and therefore most likely to benefit from more aggressive treatment, early in the assessment of stable angina.

A 10-year cardiovascular mortality of >5% (>0.5% per annum) is determined to be high risk for the purposes of implementing primary prevention guidelines.[71] However, absolute levels of what constitutes high risk and low risk are not clearly defined for those with established cardiovascular disease (CVD).[72,73] This problem is linked to difficulties in comparing risk prediction systems across different populations, determining the accuracy of individualized predictions of risk, and synthesis of multiple components of risk, often studied separately, into an estimate of risk for an individual. Added to continuously evolving public and professional perceptions of what constitutes high and low risk over the past four to five decades (when many of the initial risk predictors were defined), the reasons for this lack of definition are not easily overcome.

However, while awaiting development of a robust and portable risk prediction model which incorporates all potential aspects of risk stratification, there is an alternative pragmatic approach, based on clinical trial data. The inherent problems with bias when interpreting and generalizing clinical trial data must be recognized, but such data offer an estimate of the levels of absolute risk achievable with modern conventional treatment even in patients with proven vascular disease. This in turn facilitates the estimation of what may be accepted as constituting high, low, and intermediate risks in a contemporary setting for the purposes of determining the threshold for invasive investigation or intensified pharmacological therapy.

The rate of cardiovascular death in the PEACE[74] study was <1% per annum, whereas in 'high risk' populations such as in diabetic MICRO–HOPE[75] population and the IONA[76] population the annualized cardiovascular mortality rate was >2%. For the purposes of these guidelines, unless qualified differently in the text, if an individual with angina is determined, on the basis of a well-validated risk prediction model, to have annual cardiovascular mortality of >2% that individual is deemed high risk, whereas an annual cardiovascular mortality of <1% is considered low risk and 1–2% intermediate risk.

The clinical evaluation, the response to stress testing, the quantification of ventricular function, and the extent of CAD are the four key pieces of information to stratify patient's risk. Risk stratification generally follows a pyramidal structure, with all patients requiring risk stratification by clinical evaluation as the most basic requirement, proceeding in the majority to non-invasive assessment of ischaemia and ventricular function, and finally coronary arteriography in a selected proportion.

Risk stratification using clinical evaluation

The clinical history and physical examination can provide very important prognostic information. Electrocardiographic can be conveniently incorporated in risk stratification at this level, and the results of the laboratory tests discussed in the previous section may modify risk estimation further. Diabetes, hypertension, the metabolic syndrome, current smoking, and elevated total cholesterol (untreated or elevated despite treatment) have been shown to be predictive of adverse outcome in patients with stable angina or other populations with established coronary disease. Increasing age is an important factor to consider, as are prior MI,[77,78] symptoms and signs of heart failure,[77–79] and the pattern of occurrence (recent onset or progressive), and severity of angina, particularly if unresponsive to therapy.[80–82]

Typical angina has been shown to be a significant prognostic factor in patients undergoing coronary arteriography, however, the relation of typical angina to prognosis is mediated by its relation to the extent of coronary disease. But the pattern of angina occurrence, angina frequency and resting ECG abnormalities are independent predictors of survival and survival free of MI, and may be combined in a simple weighted score (*Figure 2*) to predict outcome, particularly in the first year after assessment. The effect of angina score on prognosis is not apparent after 3 years and is greatest when ventricular function is maintained.[72,80]

Physical examination may also help in determining risk. The presence of peripheral vascular disease (either lower limb or carotid) identifies patients at increased risk of subsequent cardiovascular events in stable angina. In addition, signs related to heart failure (which reflect LV function) convey an adverse prognosis.

Score = angina course × (1 + frequency) + ST/T abnormalities

stable = 0	(up to 5)	(6 points)
progressive = 1		
nocturnal pain = 2		
unstable = 3		

Figure 2 Prognostic angina score. The pattern of angina occurrence[80] can be used to predict prognosis.

Patients with stable angina who have resting ECG abnormalities: evidence of prior MI, LBBB, left anterior hemiblock, LVH, second or third degree AV block, or atrial fibrillation (AF) are at greater risk of future cardiovascular events than those with a normal ECG. It is possible that in an unselected population with stable angina the baseline risk is lower than in many of the studies quoted accepting that many of these studies have been conducted in patients referred for further angiographic evaluation.

Recommendations for risk stratification by clinical evaluation, including ECG and laboratory tests, in stable angina

Class I

(1) Detailed clinical history and physical examination including BMI and/or waist circumference in all patients, also including a full description of symptoms, quantification of functional impairment, past medical history, and cardiovascular risk profile (level of evidence B)
(2) Resting ECG in all patients (level of evidence B)

Risk stratification using stress testing

Stress testing can take the form of exercise or pharmacological stress with or without imaging. Prognostic information obtained from stress testing relates not only to the detection of ischaemia as a simple binary response, but also the ischaemic threshold, the extent and severity of ischaemia (for imaging techniques), and functional capacity (for exercise testing). Stress testing alone is insufficient to assess risk of future events. Risk stratification with the exercise test should be a part of a process that includes readily accessible data from clinical examination and should not take place in isolation. Thus the stress test is performed to provide additional information regarding the patient's risk status.

Symptomatic patients with suspected or known CAD should undergo stress testing to assess the risk of future cardiac events unless cardiac catheterization is urgently indicated. However, no randomized trials of stress testing have been published, and therefore the evidence base consists of observational studies only. The choice of initial stress test should be based on the patient's resting ECG, physical ability to perform exercise, local expertise, and available technologies.

Exercise ECG. The exercise ECG has been extensively validated as an important tool in risk stratification in symptomatic patients with known or suspected coronary disease. The prognostic exercise testing markers include exercise capacity and exercise-induced ischaemia (clinical and electrocardiographic). Maximum exercise capacity is a consistent prognostic marker, this measure is at least partly influenced by the extent of rest ventricular dysfunction and the amount of further LV dysfunction induced by exercise.[29,83] However, exercise capacity is also affected by age, general physical condition, comorbidites, and psychological state. Exercise capacity may be measured by maximum exercise duration, maximum MET level achieved, maximum workload achieved in Watts, maximum heart rate, and double (rate –pressure) product. The specific variable used to measure exercise capacity is less important than the inclusion of this marker in the assessment. In patients with known CAD and normal, or mildly impaired LV function, 5-year survival is higher in patients with a better exercise tolerance.[29,77,84–86]

Duke treadmill score

Exercise time in minutes *n*
mm ST-depression × 5 - *n*
Angina (not limiting × 4) - *n*
Angina (limiting × 8) - *n*

Risk		***1 year mortality***
Low risk	≥5	0.25%
Intermediate	4 to −10	1.25%
High	≤ −11	5.25%

Figure 3 Duke treadmill score.[88]

Several studies have attempted to incorporate multiple exercise variables into a prognostic score. The clinical value of stress testing is improved considerably by multivariable analysis including several exercise variables in a given patient such as the combination of heart rate at peak exercise, ST-segment depression, the presence or absence of angina during the test, peak workload and ST-segment slope.[84,87–89]

The Duke treadmill score (DTS) is a well-validated score which combines exercise time, ST deviation, and angina during exercise to calculate the patient's risk.[84,88] (*Figure 3*). In the original description of this score in a population with suspected CAD, the two thirds of patients with scores indicating low risk had a 4-year survival rate of 99% (average annual mortality rate 0.25%), and the 4% who had scores indicating high risk had a 4-year survival rate of 79% (average annual mortality rate 5%). The combination of exercise and clinical parameters, with or without the use of scores such as the DTS, has been shown to be an effective method of discriminating between high and low risk groups within a population presenting with known or suspected coronary disease.

Stress echocardiography. Stress echocardiography may also be used effectively to stratify patients according to their risk of subsequent cardiovascular events[41,90] and has an excellent negative predictive value,[91,92] with patients with a negative test having a hard event rate (death or MI) of $<0.5\%$ per year. The risk of future events is influenced both by the number of resting regional wall motion abnormalities and inducible wall motion abnormalities on stress echocardiography, with more resting abnormalities and a greater amount of inducible ischaemia associated with higher risk.[38] Identification of a high risk cohort allows for appropriate further investigation and/or intervention.

Stress perfusion scintigraphy. Normal stress myocardial perfusion images are highly predictive of a benign prognosis. Several studies involving thousands of patients have found

that a normal stress perfusion study is associated with a subsequent rate of cardiac death and myocardial infarction of <1% per year, which is nearly as low as that of the general population. The only exceptions would appear to be patients with normal perfusion images with either a high-risk treadmill ECG score or severe resting LV dysfunction.[93]

In contrast, abnormal findings on stress perfusion scintigraphy have been associated with severe CAD and subsequent cardiac events. Large stress-induced perfusion defects, defects in multiple coronary artery territories, transient post-stress ischaemic LV dilatation, and in patients studied with thallium-201, increased lung uptake on post-exercise or pharmacologic stress images are all adverse prognostic indicators.[46,94]

Exercise stress imaging offers greater prognostic information than pharmacological stress imaging because of the information regarding symptoms, exercise tolerance and haemodynamic response to exercise, which is additive to that obtained from perfusion or echocardiographic data alone.

Recommendations for risk stratification according to exercise stress ECG in stable angina in patients who can exercise
Class I

(1) All patients without significant resting ECG abnormalities undergoing initial evaluation (level of evidence B)
(2) Patients with stable coronary disease after a significant change in symptom level (level of evidence C)

Class IIa

(1) Patients post-revascularization with a significant deterioration in symptomatic status (level of evidence B)

Recommendations for risk stratification according to exercise stress imaging (perfusion or echocardiography) in stable angina in patients who can exercise
Class I

(1) Patients with resting ECG abnormalities, LBBB, >1 mm ST-depression, paced rhythm, or WPW which prevent accurate interpretation of ECG changes during stress (level of evidence C)
(2) Patients with a non-conclusive exercise ECG, but intermediate or high probability of disease (level of evidence B)

Class IIa

(1) In patients with a deterioration in symptoms post-revascularization (level of evidence B)
(2) As an alternative to exercise ECG in patients, in which facilities, cost, and personnel resources allow (level of evidence B)

Recommendations for risk stratification according to pharmacological stress imaging (perfusion or echocardiography) in stable angina
Class I

(1) Patients who cannot exercise

Other class I and II indications as for exercise stress imaging (perfusion or echocardiography) in stable angina in patients who can exercise, but where local facilities do not include exercise imaging.

Risk stratification using ventricular function
The strongest predictor of long-term survival is LV function. In patients with stable angina as LV EF declines, mortality increases. A resting EF of <35% is associated with an annual mortality rate >3% per year.[77,79,95,96] Long-term follow up data from the CASS registry showed that 72% of the deaths occurred in the 38% of the population that had either LV dysfunction or severe coronary disease. The 12-year survival rate of patients with ejection fractions >50, 35–49[96], and <35% were 73, 54, and 21%, respectively ($P < 0.0001$). The prognosis of patients with a normal ECG and low-clinical risk for severe CAD is, on the other hand, excellent.[82] Ventricular function affords additional prognostic information to coronary anatomy.

Clinical evaluation, as outlined earlier may indicate which patients have heart failure, and thus at substantially increased risk for future cardiovascular events. However, the prevalence of asymptomatic ventricular dysfunction is not inconsiderable[97–99] and has been reported to be as high as twice that of clinical heart failure, with the presence of ischaemic heart disease a major risk factor for its occurrence.

Ventricular dimensions have been shown to contribute useful prognostic information which is incremental to the results of exercise testing in a stable angina population with 2 year follow-up.[100] In a study of hypertensive patients without angina, the use of echocardiography to assess ventricular structure and function was associated with reclassification from medium/low risk to high risk in 37% of all patients,[101] and the European guidelines for the management of hypertension recommend an echocardiogram for patients with hypertension.[102] Diabetic patients with angina also require particular attention. Echocardiography in diabetic individuals with angina has the advantage of identifying LVH and diastolic as well as systolic dysfunction, all of which are more prevalent in the diabetic population. Thus, an estimation of ventricular function is desirable in risk stratification of patients with stable angina, and an assessment for ventricular hypertrophy (by echocardiography or MRI) as well as assessment of ventricular function is particularly pertinent in patients with hypertension or diabetes. For most other patients, the choice of investigation to determine ventricular function will be dependent on the other tests which have been performed or are planned, or the level of risk estimated by other methods. For example, in a patient who has a stress imaging test it may be possible to estimate ventricular function from this test without additional investigation, or a patient scheduled to have coronary arteriography on the basis of a strongly positive exercise test at low workload, in the absence of prior MI or other indications for echocardiography, may have ventricular systolic function assessed at the time of arteriography.

Recommendations for risk stratification by echocardiographic evaluation of ventricular function in stable angina
Class I

(1) Resting echocardiography in patients with prior MI, symptoms or signs of heart failure, or resting ECG abnormalities (level of evidence B)

(2) Resting echocardiography in patients with hypertension (level of evidence B)
(3) Resting echocardiography in patients with diabetes (level of evidence C)

Class IIa

(1) Resting echocardiography in patients with a normal resting ECG without prior MI who are not otherwise to be considered for coronary arteriography (level of evidence C)

Risk stratification using coronary arteriography

Despite the recognized limitations of coronary arteriography to identify vulnerable plaques which are likely to lead to acute coronary events, the extent, severity of luminal obstruction, and location of coronary disease on coronary arteriography have been convincingly demonstrated to be important prognostic indicators in patients with angina.[79,95,103,104]

Several prognostic indices have been used to relate disease severity to the risk of subsequent cardiac events; the simplest and most widely used is the classification of disease into one vessel, two vessel, three vessel, or left main (LM) CAD. In the CASS registry of medically treated patients, the 12-year survival rate of patients with normal coronary arteries was 91% compared with 74% for those with single vessel disease, 59% for those with two vessel disease, and 50% for those with three-vessel disease ($P < 0.001$).[96] Patients with severe stenosis of the LM coronary artery have a poor prognosis when treated medically. The presence of severe proximal left anterior descending (LAD) disease also significantly reduces the survival rate. The 5-year survival rate with three-vessel disease plus >95% proximal LAD stenosis was reported to be 54% compared with a rate of 79% with three-vessel disease without LAD stenosis.[104]

When appropriately used, non-invasive tests have an acceptable predictive value for adverse events. This is most true when the pre-test probability of severe CAD is low. When the estimated annual cardiovascular mortality rate is less than or equal to 1%, the use of coronary arteriography to identify patients whose prognosis can be improved is likely to be inappropriate. In contrast, it is appropriate for patients whose cardiovascular mortality risk is >2% per annum. Decisions regarding the need to proceed to arteriography in the intermediate risk group, those with an annual cardiovascular mortality of 1–2% should be guided by a variety of factors including the patient's symptoms, functional status, lifestyle, occupation, comorbidity, and response to initial therapy.

With increasing public and media interest in available medical technology, widespread access to the internet and other sources of information, patients will often have considerable information regarding investigation and treatment options for their condition. It is the duty of the physician to ensure that the patient is fully informed of their risk and the potential benefits or lack of benefit of any particular procedure and to guide their decision appropriately. Some patients may still consider medical treatment rather than intervention, or an element of doubt regarding diagnosis to be unacceptable regardless of the evidence presented to them. Coronary arteriography should not be performed in patients with angina who refuse invasive procedures, prefer to avoid revascularization, who are not candidates for PCI or CABG, or in whom it will not improve quality-of-life.

Recommendations for risk stratification by coronary arteriography in patients with stable angina

Class I

(1) Patients determined to be at high risk for adverse outcome on the basis of non-invasive testing even if they present with mild or moderate symptoms of angina (level of evidence B)
(2) Severe stable angina (Class 3 of Canadian Cardiovascular Society (CCS) Classification, particularly if the symptoms are inadequately responding to medical treatment (level of evidence B)
(3) Stable angina in patients who are being considered for major non-cardiac surgery, especially vascular surgery (repair of aortic aneurysm, femoral bypass, carotid endarterectomy) with intermediate or high risk features on non-invasive testing (level of evidence B)

Class IIa

(1) Patients with an inconclusive diagnosis on non-invasive testing, or conflicting results from different non-invasive modalities (level of evidence C)
(2) Patients with a high risk of restenosis after PCI, if PCI has been performed in a prognostically important site (level of evidence C)

A summary of the recommendations for the routine use of investigations in the evaluation of stable angina, with corresponding levels of evidence related to diagnosis and prognosis, is presented in *Tables 5* and *6*.

Special diagnostic considerations: angina with 'normal' coronary arteries

A considerable proportion of patients, especially women, who undergo coronary arteriography because of symptoms of chest pain do not have significant CAD.[105] In these patients, the features of chest pain may suggest one of the following three possibilities: (i) non-anginal pain, (ii) atypical angina including vasospastic angina, and (iii) cardiac Syndrome X.

Syndrome X

Clinical picture. Although there is no universally accepted definition of Syndrome X, to fulfil the classical description of 'Syndrome X'[106] requires the presence of the triad of

(1) typical exercise induced angina (with or without additional resting angina and dyspnoea)
(2) positive exercise stress ECG or other stress imaging modality
(3) normal coronary arteries

Chest pain occurs frequently and anginal attacks are usually encountered several times per week, but with a stable pattern. Therefore, Syndrome X resembles chronic stable angina. However, the clinical presentation of patients included in 'Syndrome X' studies is highly variable and angina at rest is often encountered in addition to exercise provoked chest pain.[107] In a subset of patients with Syndrome X, microvascular dysfunction can be demonstrated and this entity is commonly referred to as 'microvascular angina'.[108]

Arterial hypertension, either with or without associated ventricular hypertrophy, is frequently encountered in the population with chest pain and 'normal coronary arteries'. Hypertensive heart disease is characterized by endothelial

Table 5 Summary of recommendations for routine non-invasive investigations in evaluation of stable angina

Test	For diagnosis		For prognosis	
	Class of recommendation	Level of evidence	Class of recommendation	Level of evidence
Laboratory tests				
Full blood count, creatinine	I	C	I	B
Fasting glucose	I	B	I	B
Fasting lipid profile	I	B	I	B
hs C-reactive protein, homocysteine, lp(a), ApoA, ApoB	IIb	B	IIb	B
ECG				
Initial evaluation	I	C	I	B
During episode of angina	I	B		
Routine periodic ECG on successive visits	IIb	C	IIb	C
Ambulatory ECG monitoring				
Suspected arrhythmia	I	B		
Suspected vasopastic angina	IIa	C		
In suspected angina with normal exercise test	IIa	C		
Chest X-ray				
Suspected heart failure or abnormal cardiac auscultation	I	B	I	B
Suspected significant pulmonary disease	I	B		
Echocardiogram				
Suspected heart failure, abnormal auscultation, abnormal ECG, Q waves, BBB, marked ST-changes	I	B	I	B
Previous MI			I	B
Hypertension or diabetes mellitus	I	C	I	B/C
Intermediate or low risk patient not due to have alternative assessment of LV function			IIa	C
Exercise ECG				
First line for initial evaluation, unless unable to exercise/ECG not evaluable	I	B	I	B
Patients with known CAD and significant deterioration in symptoms			I	B
Routine periodic testing once angina controlled	IIb	C	IIb	C
Exercise imaging technique (echo or radionuclide)				
Initial evaluation in patients with uninterpretable ECG	I	B	I	B
Patients with non-conclusive exercise test (but adequate exercise tolerance)	I	B	I	B
Angina post-revascularization	IIa	B	IIa	B
To identify location of ischaemia in planning revascularization	IIa	B		
Assessment of functional severity of intermediate lesions on arteriography	IIa	C		
Pharmacological stress imaging technique				
Patients unable to exercise	I	B	I	B
Patients with non-conclusive exercise test due to poor exercise tolerance	I	B	I	B
To evaluate myocardial viability	IIa	B		
Other indications as for exercise imaging where local facilities favour pharmacological rather than exercise stress	II a	B	IIa	B
Non-invasive CT arteriography				
Patients with low probability of disease and non-conclusive or positive stress test	IIb	C		

dysfunction,[109] LVH, interstitial and perivascular fibrosis with diastolic dysfunction,[110] changes in myocardial and coronary ultrastructure,[111] and reduced coronary flow reserve.[112] Together or separately these changes may compromise coronary blood flow relative to myocardial oxygen demand, causing angina. For the most part, treatment in such cases should focus on control of hypertension to restore functional and structural integrity of the cardiovascular system.[113]

Prognosis. Although the prognosis in terms of mortality of patients with Syndrome X appears to be favourable,[114] the morbidity of patients with Syndrome X is high,[115,116] and the condition is frequently associated with continuing episodes of chest pain and hospital readmission.[117]There is emerging evidence that the identification of impaired endothelial dysfunction in this patient population may identify a subgroup at risk for the future development of atherosclerotic coronary disease[118] and with a less benign prognosis than previously thought.[116]

Diagnosis of Syndrome X

The diagnosis of Syndrome X may be made, if a patient with exercise induced angina has normal or non-obstructed coronary arteries by arteriography but objective signs of

Table 6 Summary of recommendations for revascularization in stable angina

Indication	For prognosis[a]		For symptoms[b]		Studies
	Class of recommendation	Level of evidence	Class of recommendation	Level of evidence	
PCI (assuming suitable anatomy for PCI, appropriate risk stratification,and discussion with the patient)					
Angina CCS Classes I to IV despite medical therapy with single vessel disease			I	A	ACME, MASS
Angina CCS Classes I to IV despite medical therapy with multi-vessel disease (non-diabetic)			I	A	RITA 2, VA-ACME
Stable angina with minimal (CCS Class I) symptoms on medication and one-, two-, or three-vessel disease but objective evidence of large ischaemia	IIb	C			ACIP
CABG (assuming suitable anatomy for surgery, appropriate risk stratification, and discussion with the patient)					
Angina and LM stem disease	I	A	I	A	CASS, European Coronary Surgery study, VA Study, Yusef meta-analysis
Angina and three-vessel disease with objective large ischaemia	I	A	I	A	
Angina and three-vessel disease with poor ventricular function	I	A	I	A	
Angina with two- or three-vessel disease including severe disease of the proximal LAD	I	A	I	A	
Angina CCS Classes I to IV with multi-vessel disease (diabetic)	IIa	B	I	B	BARI, GABI, ERACI-I, SoS, ARTs, Yusef *et al.*, Hoffman *et al.*
Angina CCS Classes I to IV with multi-vessel disease (non-diabetic)			I	A	
Angina CCS Classes I to IV despite medical therapy and single-vessel disease including severe disease of the proximal LAD			I	B	MASS
Angina CCS Classes I to IV despite medical therapy and single-vessel disease not including severe disease of the proximal LAD			IIb	B	
Angina with minimal (CCS Class I) symptoms on medication and one-, two-, or three-vessel disease but objective evidence of large ischaemia	IIb	C			ACIP

Recommendations for revascularization on symptomatic grounds take into account the range of symptomatic grades for which evidence is available and should be construed in this fashion rather than as a directive to perform revascularization across the entire range of symtomatology.

CCS = Cardiac Canadian Society.

[a]Prognosis relates to effects on mortality, cardiac or cardiovascular mortality, or mortality combined with myocardial infarction.

[b]Symptom relates to changes in angina class, exercise duration, time to angina on treadmill testing, repeat hospitalization for angina, or other parameters of functional capacity or quality-of-life.

exercise induced ischaemia (ST-depression in exercise ECG, ischaemic changes by scintigraphy). It is necessary to differentiate this pain from non-cardiac chest pain caused by oesophageal dysmotility, fibromyalgia, or costochondritis. Coronary artery spasm should be excluded by appropriate provocation tests. Endothelial dysfunction may be identified by epicardial coronary artery diameter response to acetylcholine. Invasive testing using acetylcholine provocation can serve a dual purpose by excluding vasospasm and unmasking endothelial dysfunction, which may be associated with a worse prognosis. In certain circumstances, for example in the presence of an extensive radionuclide perfusion defect or wall motion abnormality during stress testing and an angiographically irregular artery, intracoronary ultrasound may be considered to exclude missed obstructive lesions. The excellent prognosis when endothelial dysfunction is not present needs to be emphasised and the patient should be informed and reassured about the benign course of the condition.

Recommendations for investigation in patients with the classical triad of Syndrome X

Class I

(1) Resting echocardiogram in patients with angina and normal or non-obstructed coronary arteries to assess for presence of ventricular hypertrophy and /or diastolic dysfunction (level of evidence C)

Class IIb

(1) Intracoronary acetylcholine during coronary arteriography, if the arteriogram is visually normal, to assess endothelium dependent coronary flow reserve, and exclude vasospasm (level of evidence C)

Class IIb

(1) Intracoronary ultrasound, coronary flow reserve, or fractional flow reserve measurement to exclude missed obstructive lesions, if angiographic appearances are

suggestive of a non-obstructive lesion rather than completely normal, and stress imaging techniques identify an extensive area of ischaemia (level of evidence C)

Vasospastic/variant angina

Clinical picture. Patients with variant or vasospastic angina present with typically located pain, which occurs at rest, but does not, or only occasionally, occurs with exertion. Nitrates usually relieve the pain within minutes. The terms vasospastic or variant angina may be used to describe such symptoms, although 'Prinzmetal angina'[119] has also been used. Angina at rest with preserved exercise tolerance may also be associated with significant obstructive coronary disease without demonstrable vasopasm, and management is as outlined for typical symptoms. In the case of chest pain without significant coronary disease or coronary spasm, and no demonstrable ischaemia, non-cardiac causes of pain should be considered and conventional primary prevention adhered to.

A substantial proportion of patients with a history suggestive of vasopastic angina have obstructive coronary disease and in such patients vasospastic angina may coexist with typical exertional angina due to fixed coronary lesions. Vasospasm may occur in response to smoking, electrolyte disturbances (potassium, magnesium), cocaine use, cold stimulation, autoimmune diseases, hyperventilation, or insulin resistance.

Natural history and prognosis. The prognosis of vasospastic angina depends on the extent of underlying CAD. Death and myocardial infarction are not frequent in patients without angiographically significant obstructive disease, but do occur.[120] Coronary death in the population with non-obstructive lesions has been reported as ~0.5% per annum,[121] but those with spasm superimposed on stenotic lesions do significantly less well.[122]

Diagnosis of vasospastic angina

ECG. The ECG during vasospasm is classically described as showing ST-elevation.[119] In others, ST-depression can be documented,[123] whereas others may show no ST-segment shift at all.[124,125] However, as attacks tend to resolve quickly 12-lead ECG documentation tends to be difficult. Repeated 24 hours ECG monitoring may be able to capture ST-segment shifts associated with anginal symptoms in these patients.[126]

Coronary arteriography. Although the demonstration of ST-elevation at the time of angina and a normal coronary arteriogram make the diagnosis of variant angina highly likely, there is often uncertainty about the diagnosis in less well documented or clinically less straight forward cases. Moreover, there is no unanimously accepted definition of what constitutes coronary vasospasm.

Spontaneous spasm during coronary arteriography is only occasionally observed in patients with symptoms suggestive of vasospastic angina. Hence, provocation tests are commonly used to demonstrate the presence of coronary vasospasm. Hyperventilation and the cold pressor test have rather limited sensitivity for the detection of coronary spasm.[127] Thus, acetylcholine injections into the coronary artery[128] are used in most centres today but intracoronary ergonovine provocation gives similar results.[129,130] Provocative testing without coronary arteriography or provocative testing in patients with high-grade obstructive lesions on coronary arteriography are not recommended.

Recommendations for diagnostic tests in suspected vasospastic angina

Class I

(1) ECG during angina if possible (level of evidence B)
(2) Coronary arteriography in patients with characteristic episodic chest pain and ST-segment changes that resolve with nitrates and/or calcium antagonists, to determine the extent of underlying coronary disease (level of evidence B)

Class IIa

(1) Intracoronary provocative testing to identify coronary spasm in patients with normal findings or non-obstructive lesions on coronary arteriography and the clinical picture of coronary spasm. (level of evidence B)
(2) Ambulatory ST-segment monitoring to identify ST deviation (level of evidence C)

Treatment

Aims of treatment

To improve prognosis by preventing myocardial infarction and death

Efforts to prevent myocardial infarction and death in coronary disease focus primarily on reducing the incidence of acute thrombotic events and the development of ventricular dysfunction. Lifestyle changes and drug treatment play vital roles in modifying the atherosclerotic disease process and 'stabilising' coronary plaques, as well as reducing platelet activation and fibrinolytic and inflammatory abnormalities which predispose to acute plaque rupture and thrombotic occlusion. Such interventions may also halt progression or induce regression of coronary atherosclerosis. In certain circumstances, such as in patients with severe lesions in coronary arteries supplying a large area of jeopardised myocardium, revascularization offers additional opportunities to improve prognosis by improving existing perfusion or providing alternative routes of perfusion.

To minimize or abolish symptoms

Lifestyle changes, drugs, and revascularization all have a role to play in minimising or eradicating symptoms of angina, although not necessarily all in the same patient.

General management

Patients and their close associates should be informed of the nature of angina pectoris, the implications of the diagnosis, and the treatments that may be recommended. Patients should be advised to rest, at least briefly, from the activity which provoked the angina and advised regarding the use of sublingual nitrate for acute relief of symptoms. It is also useful to warn the patient of the need to protect against potential hypotension by sitting on the first number of occasions when taking sublingual nitrate and also other possible side-effects, particularly headache. The use of prophylactic nitrate to prevent predictable episodes of angina in response to exertion can be encouraged. Patients should be informed of the need to seek medical advice if angina

persists for >10–20 min after resting and/or is not relieved by sublingual nitrate.

Particular attention should be paid to the elements of lifestyle that could have contributed to the condition and which may influence prognosis, including physical activity, smoking and dietary habits. The recommendations of the Third Joint European Societies' Task Force[71] on Cardiovascular Disease Prevention in Clinical Practice should be followed.

Cigarette smoking should be strongly discouraged, and patients should be advised to adopt a 'Mediterranean' diet, with vegetables, fruit, fish and poultry being the mainstays. The intensity of change needed in the diet may be guided by the total and LDL cholesterol levels and other lipid abnormalities.[131] Those who are overweight should be put on a weight reducing diet. Alcohol in moderation may be beneficial,[132] but excessive consumption is harmful. Fish oils rich in omega-3 fatty acids (n-3 polyunsaturated fatty acids) are useful in the reduction of hypertriglyceridaemia, and in the GISSI- Prevenzione trial supplementation with one fish oil capsule (Omacor) daily was shown to reduce the risk of sudden death in patients with a recent MI.[133] Dietary intervention to achieve fish consumption at least once weekly is recommended,[134,135] Vitamin supplementation with anti-oxidant or other vitamins is not recommended.

Physical activity within the patient's limitations should be encouraged, as it may increase exercise tolerance, reduce symptoms and has favourable effects on weight, blood lipids, blood pressure, glucose tolerance, and insulin sensitivity. While the role of stress in the genesis of CAD is controversial, there is no doubt that psychological factors are important in provoking attacks of angina. Furthermore, the diagnosis of angina often leads to excessive anxiety. Reasonable reassurance is essential, and patients may benefit from relaxation techniques and other methods of stress control.

Hypertension, diabetes and other disorders

Concomitant disorders such as diabetes and hypertension should be managed appropriately. Of particular note, the Task Force report on CVD prevention[71] suggests considering a lower threshold for institution of pharmacological therapy for hypertension (130/85) for patients with established coronary heart disease (which would include patients with angina and non-invasive or invasive confirmation of coronary disease). Patients with concomitant diabetes and/or renal disease should be treated with a blood pressure goal of <130/80 mmHg.[102] Diabetes is a strong risk factor for cardiovascular complications, and should be managed carefully with good glycaemic control and attention to other risk factors.[102,136,137] Multifactorial intervention in diabetic patients may indeed reduce both cardiovascular and other diabetic complications markedly.[138] Recently the addition of pioglitizone in addition to other hypoglycaemic medication has been shown to reduce the incidence of death, MI or stroke by 16% in patients with Type II diabetes although the primary endpoint wihich included a number of vascular complications was not reduced.[139] Also anaemia or hyperthyroidism, if present, should be corrected.

Sexual intercourse

Sexual intercourse may trigger angina. Nitroglycerin prior to intercourse may be helpful. Phosphodiesterase inhibitors, such as sildenafil, tadafil or vardenafil, used in the treatment of erectile dysfunction, may bestow benefits in terms of exercise duration and can be safely prescribed to men with CAD but should *not* be used in those receiving long acting nitrates.[140]

Pharmacological treatment of stable angina pectoris

The goals of pharmacological treatment of stable angina pectoris are to improved quality-of-life by reducing the severity and/or frequency of symptoms, and to improve the prognosis of the patient.

Pharmacological therapy to improve prognosis

Antithrombotic drugs

Antiplatelet therapy to prevent coronary thrombosis is indicated, due to a favourable ratio between benefit and risk in patients with stable CAD. Low-dose aspirin is the drug of choice in most cases, and clopidogrel may be considered for some patients.

Low-dose aspirin

Aspirin remains the cornerstone of pharmacological prevention of arterial thrombosis. It acts via irreversible inhibition of platelet COX-1 and thus thromboxane production, which is normally complete with chronic dosing ≥75 mg/day.[141] The optimal antithrombotic dosage of aspirin appears to be 75–150 mg/day, as the relative risk reduction afforded by aspirin may decrease both below and above this dose range.[142]

Contrary to the antiplatelet effects, the gastrointestinal side-effects of aspirin increase at higher dosses.[141] The relative risk of suffering an intracranial haemorrhage increases by 30%,[143] but the absolute risk of such complications attributable to antiplatelet drug therapy is less than 1 per 1000 patient years of treatment with aspirin at doses ≥75 mg/day.[141,144] There is no evidence for a dose-dependence of the risk of intracranial bleeding with aspirin in the therapeutically effective dose range. In patients with atherosclerotic vascular disease, where the main aetiology of stroke is ischaemic, the net effect of aspirin treatment regarding stroke is clearly beneficial.,[141,144] Thus, the dosage of aspirin should be the lowest effective one in order to optimize the balance between therapeutic gains and gastrointestinal side-effects during chronic therapy.

Cyclooxygenase-(COX)-2 inhibitors and NSAID's

COX-2 inhibition reduces the production of prostacyclin, which has vasodilatory and platelet inhibiting effects. Attenuation of prostacyclin formation may predispose to elevated blood pressure, accelerated atherogenesis, and thrombosis upon plaque rupture.[145] The recent withdrawal of rofecoxib (Vioxx), a highly selective COX-2 inhibitor, was caused by findings of an increased risk of serious coronary events in a placebo-controlled trial of cancer prevention.[146] An increased risk of suffering fatal or non-fatal MI was also found in a meta-analysis of other randomized trials with rofecoxib.[147] Thus, there are indications from studies with several COX-2 inhibitors that they may increase the risk of coronary thrombotic events in patient populations with different levels of cardiovascular risk. In addition, COX-2 inhibition increases the risk of suffering stroke, heart failure and hypertension.[148] The use of

unopposed COX-2 inhibition (i.e. without effective simultaneous platelet COX-1 inhibition) should thus be avoided in patients with stable angina pectoris.

Non-selective, reversible COX inhibitors (NSAID) treatment should, when this is indicated for other reasons, be combined with low-dose aspirin to assure effective platelet inhibition in patients with stable angina pectoris. In such circumstances ibuprofen should be avoided, since this NSAID prevents aspirin from irreversibly acetylating the COX-1 enzyme of platelets, as may naproxen. Diclofenac is a relatively COX-2 selective NSAID and therefore a poor platelet inhibitor,[149] but does not interfere with the antiplatelet effects of aspirin and may be used in combination with aspirin.

Clopidogrel

Clopidogrel and ticlopidine are thienopyridines which act as non-competitive ADP receptor antagonists, and which have antithrombotic effects similar to aspirin.[141] Ticlopidine has been replaced by clopidogrel due to the risk of neutropenia and thrombocytpenia, and more symptomatic side-effects with ticlopidine. The main study documenting clopidogrel use in stable CAD is CAPRIE,[150] which included three equally large groups of patients with previous MI, previous stroke or peripheral vascular disease (PVD). Compared with aspirin 325 mg/day, clopidogrel 75 mg/day was slightly more effective (ARR 0.51% per year; $P = 0.043$) in preventing cardiovascular complications in high risk patients.[150] When comparing outcomes in the three subgroups of patients enrolled in CAPRIE the benefit with clopidogrel appeared in the PVD subgroup only.[150] Gastrointestinal haemorrhage was only slightly less common with clopidogrel when compared with aspirin treatment (1.99 vs. 2.66% during 1.9 years of treatment), despite the relatively high aspirin dose.[150] The CAPRIE study did not include patients with aspirin intolerance, and we do not know the risk of gastrointestinal bleeding during clopidogrel when compared with placebo treatment. Clopidogrel is much more expensive than aspirin, but may be considered in aspirin intolerant patients with significant risks of arterial thrombosis. Gastrointestinal intolerance may, however, be handled differently (see below). After coronary stenting or an acute coronary syndrome clopidogrel may be combined with aspirin during a finite period of time, but combination therapy is currently not warranted in stable angina pectoris.

One much discussed reason for variability of antiplatelet responses to clopidogrel is drug-drug interactions, as clopidogrel forms its active metabolite(s) via CYP3A4 mediated metabolism, however, the data is inconsistent. So far, observational post-hoc analyses of outcomes among patients receiving maintenance co-treatment with clopidogrel + an interacting statin have not shown differences in outcome, and there are no properly designed prospective studies that address the issue.

Antiplatelet therapy in patients with gastrointestinal intolerance to aspirin

Aspirin causes dose-related gastric mucosal damage which may cause symptoms and increase the incidence of gastrointestinal bleeding. Clopidogrel is an alternative antiplatelet without direct effects on the gastric mucosa, and may cause less dyspeptic symptoms, but gastrointestinal haemorrhages may increase with any antiplatelet treatment. The size of this effect with clopidogrel is not known in the absence of data from placebo-controlled trials. In cases of mucosal erosions due to aspirin or NSAID therapy, these may be alleviated by inhibiting gastric acid secretion. Eradication of *Helicobacter Pylori* infection, if present, also reduces the risk of aspirin related gastorintestinal bleeding.[151] A recent study showed that the addition of esomeprazole to aspirin (80 mg/day) was better than switching to clopidogrel for the prevention of recurrent ulcer bleeding in patients with ulcers and vascular disease.[152]

Dipyridamole and anticoagulants

Dipyridamole is not recommended for antithrombotic treatment in stable angina due to poor antithrombotic efficacy[142] and the risk of worsening anginal symptoms due to coronary steal phenomena. Anticoagulant drugs (warfarin or thrombin inhibitors), which are combined with aspirin in certain high risk patients, such as post myocardial infarction, are not indicated in the general stable angina population without a separate indication such as AF for example.

Aspirin resistance

Possible problems related to 'aspirin resistance',[153,154] and also 'clopidogrel resistance'[155] are of considerable interest but in the absence of clear conclusions from this area of research and a 'gold standard' with which to evaluate aspirin resistance, further research is needed before management schemes can be implemented.

Lipid-lowering drugs

Statin treatment reduces the risk of atherosclerotic cardiovascular complications in both primary and secondary prevention settings.[156] In patients with atherosclerotic vascular disease simvastatin and pravastatin[157–159] reduce the incidence of serious cardiovascular complications by some 30%. Subgroup analyses indicate beneficial effects also in diabetic patients with vascular disease and benefits of statin therapy have also been demonstrated in the elderly (>70 years)[160,161] In diabetic patients without manifest vascular disease simvastatin 40 mg/day[162] and atorvastatin 10 mg/day[163] provided similar primary protection against major cardiovascular events. Reductions in major cardiovascular events were also observed in the placebo-controlled Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA)[164] which evaluated atorvastatin treatment in the primary prevention of CHD in hypertensive patients with TC levels $\leq$6.5 mmol/L. No trial has been performed specifically in patients with stable angina pectoris, but such patients constituted significant proportions of the trials mentioned. In HPS, for example, 41% of patients were post-MI and 24% had other CAD.

Statins lower cholesterol effectively,[156] but mechanisms other than cholesterol synthesis inhibition, such as anti-inflammatory and antithrombotic effects may contribute to the cardiovascular risk reduction. In patients with stable angina it has been shown that 7 days pretreatment with atorvastatin 40 mg/day when compared with placebo before PCI reduced procedural myocardial injury, as assessed by biochemical markers.[165] Such myocardial protection by short-term, high-dose atorvastatin treatment

may be related to non-lipid effects of the statin treatment. Similar relative benefits of long-term statin therapy have been observed in patients with different pretreatment levels of serum cholesterol, even in the 'normal' range.[161,163] Thus, recommendations to treat with statins may be guided as much by the patients level of cardiovascular risk as by the cholesterol level (within the normal to moderately elevated range). The risk associated with cholesterol increases log-linearly from low normal levels,[156] and it is therefore difficult to evaluate the relative importances of cholesterol lowering and other effects of statin treatment for the treatment benefits observed.

Current European prevention guidelines suggest a target value of $<$4.5 mmol/L (175 mg/dL) for TC and 2.5 mmol/L (96 mg/dL) for LDL cholesterol in patients with established CHD or even those who remain at persistently high multifactorial risk ($>$5% risk of fatal cardiovascular events over 10 years). However therapy solely directed at cholesterol goals may not fully exploit the benefit of statin therapy.

Statin therapy should always be considered for patients with stable CAD and stable angina, based on their elevated level of risk and evidence of benefit of cholesterol lowering within the 'normal' range.[166] Therapy should aim at statin dosages documented to reduce morbidity/mortality in clinical trials. If this dose is not sufficient to achieve the target TC and LDL levels as mentioned above the dose of statin therapy may be increased as tolerated to achieve the targets. The daily statin dosages with solid documentation in the above-mentioned studies are simvastatin 40 mg, pravastatin 40 mg and atorvastatin 10 mg. Recently, high-dose atorvastatin treatment (80 mg daily) has been shown to reduce the risk of cardiovascular events when compared with 10 mg atorvastatin in patients with stable CAD.[167] The increased efficacy of high-dose atorvastatin treatment was accompanied by six-fold increase (from 0.2 to 1.2%; $P < 0.001$) in enzymatic signs of liver damage, but no discernible increase in myalgia. High-dose atorvastatin therapy should be reserved for high risk patients.

Statin treatment is associated with few side-effects, but skeletal muscle damage (symptoms, CK elevations and, rarely, rhabdomyolysis) may occur, and liver enzymes should also be monitored after initiation of therapy. Gastrointestinal disturbances may limit the dosage. If statins are poorly tolerated at high doses, or lipid control is not achieved with the highest statin dose, reduction of the statin dose and the addition of the cholesterol absorption inhibitor, ezetimibe, may afford adequate reduction of cholesterol.[168] Effects on morbidity and mortality of such combination treatment have, however, not yet been documented.

Other lipid lowering drugs, eg fibrates, prolonged release nicotinic acid and their combinations with statins and other hypolipidaemics may be needed to control the lipid levels among patients with severe dyslipidaemia. This is especially true of those with low levels of HDL-cholesterol and high triglycerides. Torcetrapib is a new agent which has been shown to raise HDL effectively,[169] but as yet there is insufficient evidence to make universal recommendations regarding target HDL or triglyceride levels to be achieved by pharmacotherapy to in the general population with angina. Adjunctive therapy to statin therapy may be considered on an individualised basis in patients who have severe dyslipidaemia and remain at high risk after conventional measures (estimated cardiovascular mortality $>$2% per annum).

Angiotensin-converting enzyme-inhibitors

Angiotensin-converting enzyme (ACE)-inhibitors are well established for the treatment of hypertension and heart failure. Because of observed reductions in myocardial infarction and cardiac mortality in trials of ACE-inhibitors for heart failure and post MI, ACE-inhibitors have also been investigated as secondary preventive therapy for patients with coronary disease without heart failure.[170,171–74]

The relative risk reductions for composite primary endpoints were in the order of 20% in the HOPE and EUROPA studies, whereas the PEACE study found no significant risk reduction with ACE inhibition. The results of the three studies are unfortunately not directly comparable due to different selections of endpoints.

A possible explanation for this difference in outcomes might be differences between the three ACE-inhibitors and/or the relative dosages used. Overall PEACE patients were at lower absolute risk than the HOPE or EUROPA patients. These differences in baseline risk and non-study related therapy may have contributed importantly to the differences in cardiovascular outcome with ACE-inhibitor therapy. The relative effects of ramipril and perindopril on cardiovascular outcome were similar in a high risk population and an intermediate population respectively, although for obvious reasons the absolute risk reduction was greater in the population at highest absolute risk.

The blood pressure lowering effects of ramipril and perindopril when compared with placebo probably contributed to the risk reduction in the HOPE and EUROPA studies, but additional cardioprotection may also be afforded by ACE-inhibitors.[172] Furthermore, ACE inhibition is well established in the treatment of heart failure or LV dysfunction,[173] and in the treatment of diabetic patient.[136] Thus, it is appropriate to consider ACE-inhibitors for the treatment of patients with stable angina pectoris and co-existing hypertension, diabetes, heart failure, asymptomatic LV dysfunction and post-MI. In angina patients without co-existing indications for ACE-inhibitor treatment the anticipated benefit of treatment (possible absolute risk reduction) should be weighed against costs and risks for side-effects, and the dose and agent used of proven efficacy for this indication.

Hormone replacement therapy (HRT)

Epidemiological evidence suggested substantial cardiovascular benefits of postmenopausal use of HRT. More recently, however, properly designed prospective, double-blind, placebo-controlled trials have shown that HRT with a combination of oral oestrogen/progestin offered no cardiovascular benefit among women with established disease,[174,175] and that there is an *increased* risk of developing CVD in primary prevention, and also an increased risk of suffering breast cancer.[176] Primary prevention with unopposed estrogen therapy in hysterectomized women offered no cardiovascular protection.[177] New guidelines therefore recommend against routine use of HRT for chronic conditions[178] and current users have been advised to taper doses downwards towards discontinuation.[179]

Beta-blockers

The risk of suffering cardiovascular death or myocardial infarction was reduced by some 30% in post-MI trials with beta blockers.[180] A recent meta-regression analysis of the effects of different beta-blockers on mortality found non-

significant benefits of acute treatment, but a significant 24% relative reduction of mortality with long term secondary preventive treatment.[181] Beta-blockers with intrinsic sympathomimetic activity appeared to provide less protection, and it was pointed out that the most frequently prescribed agent, atenolol, had poor documentation regarding mortality after MI.[181] It has been extrapolated from the post-MI trials that beta-blockers may be cardioprotective also in patients with stable coronary disease. However, this has not been proven in a placebo-controlled trial. The beta-blocker trials post-MI were performed before the implementation of other secondary preventive therapy, such as treatment with statins and ACE-inhibitors, which leaves some uncertainty regarding their efficacy on top of a 'modern' treatment strategy.

Large beta-blocker studies in stable angina, the APSIS[7] and TIBET[6] studies, did not show a significant difference in outcome between patients treated with beta-blockade or calcium channel blockers, either nifedipine or verapamil. A smaller study (≈300 patient years) in patients with minimal or no symptoms of angina compared atenolol and placebo treatment (the ASIST trial), and showed a higher incidence of a combined endpoint, which included symptoms requiring treatment in the placebo group.[182] This confirmed the beneficial anti-anginal effects of a beta-blocker, but does not show if treatment alters the prognosis of patients with stable angina pectoris.

Beta-1 blockade by metoprolol or bisoprolol have been shown to effectively reduce cardiac events in patients with congestive heart failure.[183,184] Carvedilol, a non-selective beta-blocker that also blocks alpha-1 receptors, also reduces risk of death and hospitalisations for cardiovascular causes in patients with heart failure.[185] To conclude there is evidence of prognostic benefit from the use of beta-blockade in patients with angina who have suffered prior MI or have heart failure, and extrapolated from these data beta-blockers are suggested as a first line anti-anginal therapy in patients without contraindications.

Calcium channel blockers

Heart rate lowering CCB's may improve the prognosis of post-MI patients, as shown in the DAVIT II study for verapamil[186] and in a subgroup analysis of patients without signs of heart failure in the MDPIT study for diltiazem.[187] However older trials of short-acting nifedipine showed no benefit regarding hard endpoints among patients with CAD, and even an increased risk of dying with high doses of the drug.[188] This sparked an intense 'calcium antagonist debate' which pointed out the inappropriateness of treatment with short-acting vasodilator drugs such as dihydropyridine CCB's. A meta-analysis of the safety of nifedipine in stable angina pectoris suggested that the drug was safe.[189]

The recently published ACTION trial,[190] which compared treatment with long-acting nifedipine and placebo during 4.9 years of follow-up in 7665 patients with stable angina pectoris showed no benefit of treatment with long-acting nifedipine when compared with placebo with regard to composite endpoints including death, MI, refractory angina, debilitating stroke and heart failure. Nifedipine treatment tended to increase the need for peripheral revascularization (HR 1.25; $P = 0.073$), but reduced the need for coronary bypass surgery (HR 0.79; $P = 0.0021$). The authors concluded that nifedipine treatment is safe and reduces the need for coronary interventions.[190] However, the lack of beneficial effects of nifedipine on hard endpoints may not satisfy the requirements for 'cardiovascular safety'. The CAMELOT study[191] compared treatment with amlodipine, enalapril or placebo in 1991 patients with stable CAD and normal blood pressure during 2 years of follow-up. Amlodipine and enalapril treatment lowered blood pressure equally and tended to reduce the incidence of 'hard' endpoints similarly, although these results were not significant.

To conclude there is no evidence to support the use of calcium channel blockers for prognostic reasons in uncomplicated stable angina, although rate lowering calcium channel blockers may be used as an alternative to beta blockers post myocardial infarction in patients without heart failure who do not tolerate beta blockers.

Recommendations for pharmacological therapy to improve prognosis in patients with stable angina

Class I

(1) Aspirin 75 mg daily in all patients without specific contraindications (ie active GI bleeding, aspirin allergy or previous aspirin intolerance) (level of evidence A)
(2) Statin therapy for all patients with coronary disease (level of evidence A)
(3) ACE-inhibitor therapy in patients with coincident indications for ACE-inhibition, such as hypertension, heart failure, LV dysfunction, prior MI with LV dysfunction, or diabetes (level of evidence A)
(4) Oral beta blocker therapy in patients post-MI or with heart failure (level of evidence A)

Class IIa

(1) ACE-inhibitor therapy in all patients with angina and proven coronary disease (level of evidence B)
(2) Clopidogrel as an alternative antiplatelet agent in patients with stable angina who cannot take aspirin eg Aspirin allergic (level of evidence B)
(3) High-dose statin therapy in high risk (>2% annual CV mortality) patients with proven coronary disease (level of evidence B)

Class IIb

(1) Fibrate therapy in patients with low HDL and high triglycerides who have diabetes or the metabolic syndrome (level of evidence B)

Pharmacological treatment of symptoms and ischaemia

Symptoms of angina pectoris and signs of ischaemia (also silent ischaemia) may be reduced by drugs that reduce myocardial oxygen demand and/or increase blood flow to the ischaemic area. Commonly used anti-anginal drugs are beta-blockers, calcium antagonists and organic nitrates.

Short-acting nitrates

Rapidly acting formulations of nitroglycerin provide effective symptom relief in connection with attacks of angina pectoris, and may be used for 'situational prophylaxis'. The pain relieving and anti-ischaemic effects are related to venodilatation and reduced diastolic filling of the heart (reduced intracardiac pressure), which promotes subendocardial perfusion. Coronary vasodilatation and antagonism

of coronary vasospasm may contribute. Nitrate tolerance (see below) blunts responses to short-acting nitroglycerin, and should be avoided.

Nitroglycerin causes dose-dependent vasodilator side-effects, such as headache and flushing. Overdosing may cause postural hypotension and reflexogenic cardiac sympathetic activation with tachycardia, leading to 'paradoxical' angina. An attack of angina that does not respond to short-acting nitroglycerin should be regarded as a possible myocardial infarction. Thus, patients should be carefully instructed about how to use short-acting nitroglycerin. Short-acting nitrate consumption is a simple and good measure of treatment effects with other anti-anginal drugs.

Long-acting nitrates

Treatment with long-acting nitrates reduces the frequency and severity of anginal attacks, and may increase exercise tolerance. Studies of long acting nitrate treatment after myocardial infarction have failed to show prognostic benefit.

Due to nitrate tolerance, patients treated with long-acting nitrates should have a 'nitrate free' interval each day to preserve the therapeutic effects. This may be achieved with appropriate timing of doses of intermediate acting ISDN or with formulations of ISMN that provide a suitable plasma concentration profile. Continuous transdermal nitroglycerin therapy is not effective and patients should remove the patches during part of the day or at night to achieve the nitrate free interval.

Beta-blockers

Beta-blockers are effective in reducing anginal symptoms and ischaemia.[40,192–194] They reduce oxygen demand by reducing heart rate and contractility, and by reducing blood pressure. Resting and exercise heart rate will be reduced by most beta-blockers except those with partial agonist activity where only the exercise heart rate is reduced. Perfusion of ischaemic areas may be improved by prolonging diastole (i.e. the perfusion time), and by 'reverse coronary steal' due to increased vascular resistance in non-ischaemic areas.

Beta-1 selective agents are preferred due to advantages concerning side-effects and precautions when compared with non-selective beta-blockers. Commonly used beta-1 blockers with good documentation as anti-anginal drugs are metoprolol, atenolol and bisoprolol. To achieve 24 h efficacy a beta-1 blocker with a long half-life (e.g. bisoprolol) or a formulation providing an extended plasma concentration profile (e.g. metoprolol CR) may be used. For atenolol (with a plasma half life of 6–9 h), twice daily dosing may be better, but increasing the dose also extends the duration of action. Target doses for full anti-anginal effects are: bisoprolol 10 mg o.d., metoprolol CR 200 mg o.d., atenolol 100 mg/day o.d. (or 50 mg b.i.d.). The degree of beta-blockade may be assessed by exercise testing. Beta-blockers are effective anti-anginal drugs, which increase exercise tolerance, and decrease symptom frequency and short-acting nitrate consumption. However, symptoms may increase on beta-blockade in patients with vasospastic angina.

Side-effects of beta-blockade include cold extremities and symptomatic bradycardia, both of which are related to cardiac inhibition, and increased respiratory symptoms in asthma/COPD (less common with beta-1 selective agents). Beta-blockers may cause fatigue, but only 0.4% of patients in trials discontinued treatment for this reason.[195] Similarly, depression was not increased among beta-blocker treated patients, and sexual dysfunction was only found in 5 per 1000 patient years of treatment (leading to discontinuation in 2/1000).[196] Quality-of-life, which has been extensively studied in the treatment of hypertension, is well preserved with beta-blocker treatment of hypertensive patients,[196,197] but this has not been systematically studied in patients with stable angina.[198]

Calcium channel blockers

Calcium channel blockers (CCB's) are also well established anti-anginal agents.[40,191–194] This is a heterogeneous class of drugs which dilate coronary and other arteries by inhibiting calcium influx via L-type channels. Non-selective or heart rate lowering CCB's (verapamil and diltiazem) also to some degree reduce myocardial contractility, heart rate and A-V nodal conduction.[40,192] Even vaso-selective dihydropyridine CCB's (e.g. nifedipine, amlodipine and felodipine) may cause some cardiodepression, but this is counteracted by reflexogenic cardiac sympathetic activation with slight increases in heart rate which subside over time. However, signs of sympathetic activation may be seen even after months of treatment with a dihydropyridine CCB.[199]

Long-acting CCB's (e.g. amlodipine) or sustained release formulations of short-acting CCB's (e.g. nifedipine, felodipine, verapamil and diltiazem) are preferred, to minimize fluctuations of plasma concentrations and cardiovascular effects.[200] Side-effects are also concentration-dependent, and mainly related to the arterial vasodilator responses (headache, flushing and ankle oedema); these effects are more pronounced with dihydropyridine CCB's. Verapamil may cause constipation.

The anti-anginal effects of CCB's are related to decreased cardiac work due to systemic vasodilatation, as well as coronary vasodilatation and counteraction of vasospasm.[40,192] CCB's are especially effective in patients with vasospastic (Prinzmetal) angina,[40] but in some patients CCB's may, however, increase ischaemia.[201]

The CAMELOT study[191] showed that the anti-anginal effects of amlodipine when compared with placebo treatment significantly reduced hospitalisation for angina, as well as the need for revascularization during a 2-year follow-up. Enalapril treatment was not associated with similar effects on ischemia-related outcomes. In the CAPE study[202] treatment with amlodipine when compared with placebo resulted in a modest, but significant further reduction of ischemia on Holter monitoring (placebo effects were rather pronounced) after 7 weeks of treatment. The patients reported greater reductions of anginal attacks (70 vs. 44%) and a more pronounced reduction of nitroglycerin consumption (67 vs. 22%) during week 10 of amlodipine when compared with placebo treatment. The side-effect profile of amlodipine was favourable in both CAMELOT and CAPE. In the ACTION study, although not associated with a reduction in the primary endpoint (death, acute myocardial infarction, refractory angina, new overt heart failure, debilitating stroke and peripheral revascularization), nifedipine therapy was associated with reduced need for coronary bypass surgery HR 0.79, $P = 0.002$.[190]

The anti-anginal and anti-ischaemic effects of CCB's are additive to those of beta-blockers in many, but not all patients. Dihydropyridine CCB's are suitable for combination

with beta-blockers, which counteract the reflexogenic cardiac sympathetic activation. Heart rate lowering CCB's may cause conduction disturbances in predisposed patients treated with beta-blockers. All CCB's may precipitate heart failure in predisposed patients; attempts to use dihydropyridine CCB's for vasodilator treatment of heart failure have not been successful. However, amlodipine may be used for the treatment of angina or hypertension in patients with compensated heart failure if not controlled by other therapy (i.e. nitrates, beta-blockers).[203]

Comparison of beta-blocker and calcium antagonist (CCB) treatment in stable angina

The IMAGE study[204] compared patients with stable angina treated with metoprolol CR 200 mg o.d. or nifedipine SR 20 mg b.i.d. during 6 weeks (140 patients in each group). Both metoprolol and nifedipine prolonged exercise tolerance over baseline levels, with greater improvement in patients receiving metoprolol ($P < 0.05$). Responses to the two drugs were variable, and were difficult to predict. In the APSIS study, treatment with verapamil SR for 1 month was slightly more effective than metoprolol CR in increasing exercise tolerance.[205] However, although exercise induced ischaemia was predictive of cardiovascular events in the study,[205] short term treatment effects on exercise induced ischaemia did not independently predict improvement in long-term outcome.

The TIBBS study[206] showed anti-ischaemic and anti-anginal effects of both bisoprolol and nifedipine, but bisoprolol was clearly more effective. The TIBET study compared the effects of atenolol, nifedipine or their combination on exercise induced ischaemia and the total ischaemic burden in a double-blind, parallel group design. Both medications, alone and in combination, caused significant improvements in exercise parameters and significant reductions in ischaemic activity during daily activities when compared with placebo but there were no significant differences between groups for any of the measured ischaemic parameters. There were significantly more withdrawals due to side-effects in the nifedipine group when compared with the atenolol and the combination groups.[6,207] Meta-analyses comparing effects of beta-blockers and CCB's in stable angina pectoris indicate that beta-blockers are more effective than CCB's in reducing anginal episodes,[208] but that effects on exercise tolerance and ischaemia of the two drug classes are similar.[40,208]

Thus, in the absence of prior MI, the available data suggest that the choice between a beta-blocker and a CCB for anti-anginal treatment may be guided by individual tolerance and the presence of other disease and co-treatment. If these factors are equally weighted a beta-blocker is recommended as the first choice.

Comparison of nitrates with beta-blockers or CCB's

There are relatively few studies comparing anti-anginal and anti-ischaemic effects of long-acting nitrates with beta-blockers or CCB's, and there is no documentation concerning possible effects of nitrates on morbidity in stable angina pectoris.[208] There were non-significant trends towards less nitroglycerin use with beta-blockers, and fewer angina episodes per week with CCB's compared with long-acting nitrates in the meta-analysis by Heidenreich *et al*.[208] Thus long-acting nitrates have no overall therapeutic advantages over beta-blockers or CCB's.

Potassium channel openers

The principal agent in this class, nicorandil, has a dual mechanism of action, and is a potassium channel activator with a nitrate moiety and nitrate like effects.[209] Nicorandil is administered at a usual dose of 20 mg b.i.d for the prevention of angina. Tolerance to the anti-anginal effect may develop with chronic dosing but cross-tolerance with nitrates does not seem to be a problem. In addition to its anti-anginal properties, nicorandil is thought to have cardioprotective properties. The Impact Of Nicorandil in Angina (IONA) trial showed a significant reduction of major coronary events in stable angina patients treated with nicorandil when compared with placebo as add-on to conventional therapy.[76] However, the result was driven by effects of nicorandil on 'hospital admission for cardiac chest pain', and the risk reduction regarding cardiac death or non-fatal MI during 1.6 years of treatment was non significant[76] thus the value of the treatment effect has been argued.[210] Nicorandil is not available in all countries.

Other agents

Sinus node inhibitors, such as ivabradine, have negative chronotropic effects both at rest and during exercise, have proven anti-anginal efficacy and may be used as an alternative agent in patients who do not tolerate beta-blockade.[171,211,212]

Metabolically acting agents protect from ischaemia by increasing glucose metabolism relative to that of fatty acids. Both trimetazidine[213,214] and ranolazine,[215,216] have been shown to have anti-anginal efficacy. They may be used in combination therapy with haemodynamically acting agents, as their primary effect is not through reduction in heart rate or blood pressure. Trimetazidine has been available for several years, but not in all countries. Ranolazine, although under intensive investigation is not yet licensed for use by the EMEA. Whether these drugs influence the prognosis of patients with stable angina has not been determined. Molsidomine is a vasodilator with an action similar to that of organic nitrates and in the appropriate dosage is an effective anti-ischaemic and anti-anginal agent.[217] It is not available in all countries.

Recommendations for pharmacological therapy

Anti-anginal drug treatment should be tailored to the needs of the individual patient, and should be monitored individually. Short acting nitrate therapy should be prescribed for all patients for immediate relief of acute symptoms as tolerated. Although different types of drugs have been shown to have additive anti-anginal effects in clinical trials, this may not necessarily be so in the individual patient. More intense anti-anginal treatment may also cause problems, as it has been shown that three anti-anginal drugs may provide less symptomatic protection than two drugs.[218,219] Thus, the dosing of one drug should be optimized before adding another one, and it is advisable to switch drug combinations before attempting a three drug regimen. Poor adherence is always a factor to consider when drug therapy is unsuccessful.

The following strategy (see algorithm in *Figure 4*) is recommended for anti-anginal drug treatment in patients who

are considered suitable for medical management after initial evaluation and risk stratification: The following recommendations which pertain to anti-anginal theory and follow, the level of evidence refers to anti-anginal or anti-ischaemic efficacy unless stated otherwise.

Recommendations for pharmacological therapy to improve symptoms and/or reduce ischaemia in patients with stable angina

Class I

(1) Provide short-acting nitroglycerin for acute symptom relief and situational prophylaxis, with appropriate instructions on how to use the treatment (level of evidence B)
(2) Test the effects of a beta-1 blocker, and titrate to full dose; consider the need for 24 h protection against ischaemia (level of evidence A)
(3) In case of beta-blocker intolerance or poor efficacy attempt monotherapy with a calcium channel blocker (level of evidence A), long acting nitrate (level of evidence C), or nicorandil (level of evidence C)
(4) If the effects of beta-blocker monotherapy are insufficient, add a dihydropyridine calcium channel blocker (level of evidence B)

Class IIa

(1) In case of beta-blocker intolerance try sinus node inhibitor (level of evidence B)
(2) If CCB monotherapy or combination therapy (CCB with beta-blocker) is unsuccessful, substitute the CCB with a long-acting nitrate or nicorandil. Be careful to avoid nitrate tolerance (level of evidence C)

Class IIb

(1) Metabolic agents may be used where available as add on therapy, or as substitution therapy when conventional drugs are not tolerated (level of evidence B)

Consider triple therapy only if optimal two drug regimens are insufficient, and evaluate the effects of additional drugs carefully. Patients whose symptoms are poorly controlled on double therapy should be assessed for suitability for revascularization, as should those who express a strong preference for revascularization rather than pharmacological therapy. The ongoing need for medication to improve prognosis irrespective of revascularization status, and the balance of risk and benefit on an individual basis, should be explained in detail. Despite the array of therapeutic options outlined, the management of refractory angina continues to pose a challenge and management options in such cases are outlined in a separate section below.

Special therapeutic considerations: cardiac Syndrome X and vasospastic angina

Treatment of Syndrome X. Treatment should focus on symptomatic relief.[220] As nitrates are effective in about half of the patient it is reasonable to start treatment with long acting nitrates. If symptoms persist, calcium-antagonists or beta-blockers may be added. Although α-adrenergic blockade increases vasodilator reserve in patients with Syndrome X α-adrenergic blocking agents are clinically inefficient.[221,222] There are reports that other drugs such as nicorandil and trimetazidine might be helpful in some patients.

ACE-inhibitors and statins are helpful to reverse underlying endothelial dysfunction and should be actively considered for patients with Syndrome X as part of their risk factor management. There is some data to suggest that ACE-inhibitors and statins may also be beneficial in reducing exercise induced ischaemia in this population.

The challenge of achieving long lasting therapeutic effects in patients with Syndrome X requires a multidisciplinary approach.[223] This might include analgesic intervention using imipramine or aminophylline, psychological intervention, electrostimulation techniques, and physical training. Some studies of transdermal hormone replacement therapy[224,225] in postmenopausal patients have shown an improvement in endothelial function and symptoms, but in the light of recent trials documenting adverse cardiovascular outcomes with the use of HRT, caution is advised in prescription of HRT for this purpose.

Recommendations for pharmacological therapy to improve symptoms in patients with Syndrome X

Class I

(1) Therapy with nitrates, β-blockers, and calcium antagonists alone or in combination (level of evidence B)
(2) Statin therapy in patients with hyperlipidaemia (level of evidence B)
(3) ACE-inhibition in patients with hypertension (level of evidence C)

Class IIa

(1) Trial of therapy with other anti-anginals including nicorandil and metabolic agents (level of evidence C)

Class IIb

(1) Aminophylline for continued pain despite Class I measures (level of evidence C)
(2) Imipramine for continued pain despite Class I measures (level of evidence C)

Treatment of vasopastic angina. Removal of precipitating factors such as cessation of smoking is essential.[226] The main elements of drug therapy are nitrates and calcium antagonists. Whereas nitrates are highly effective in abolishing acute vasospasm they are not as successful in preventing attacks of resting angina.[129] Calcium channel blockers are more effective in alleviating the signs and symptoms of coronary spasm and treatment should be aimed at using high doses (up to 480 mg/day verapamil, up to 260 mg/day diltiazem, up to 120 mg/day nifedipine). However, calcium antagonists achieve a complete resolution of symptoms in only 38% of patients.[129] In most patients, a combination therapy with long acting nitrates and high doses of calcium antagonists will result in an improvement of symptoms. The role of α-blockers is controversial but occasional therapeutic benefit has been reported.[227] Nicorandil, a potassium channel activator, may also be useful in occasional patients with refractory vasospastic angina.[228]

Spontaneous remission of spasmodicity occurs in about half of western people following medical treatment for at least 1 year.[229] Thus, it is acceptable to taper and discontinue treatment 6–12 months after angina has disappeared

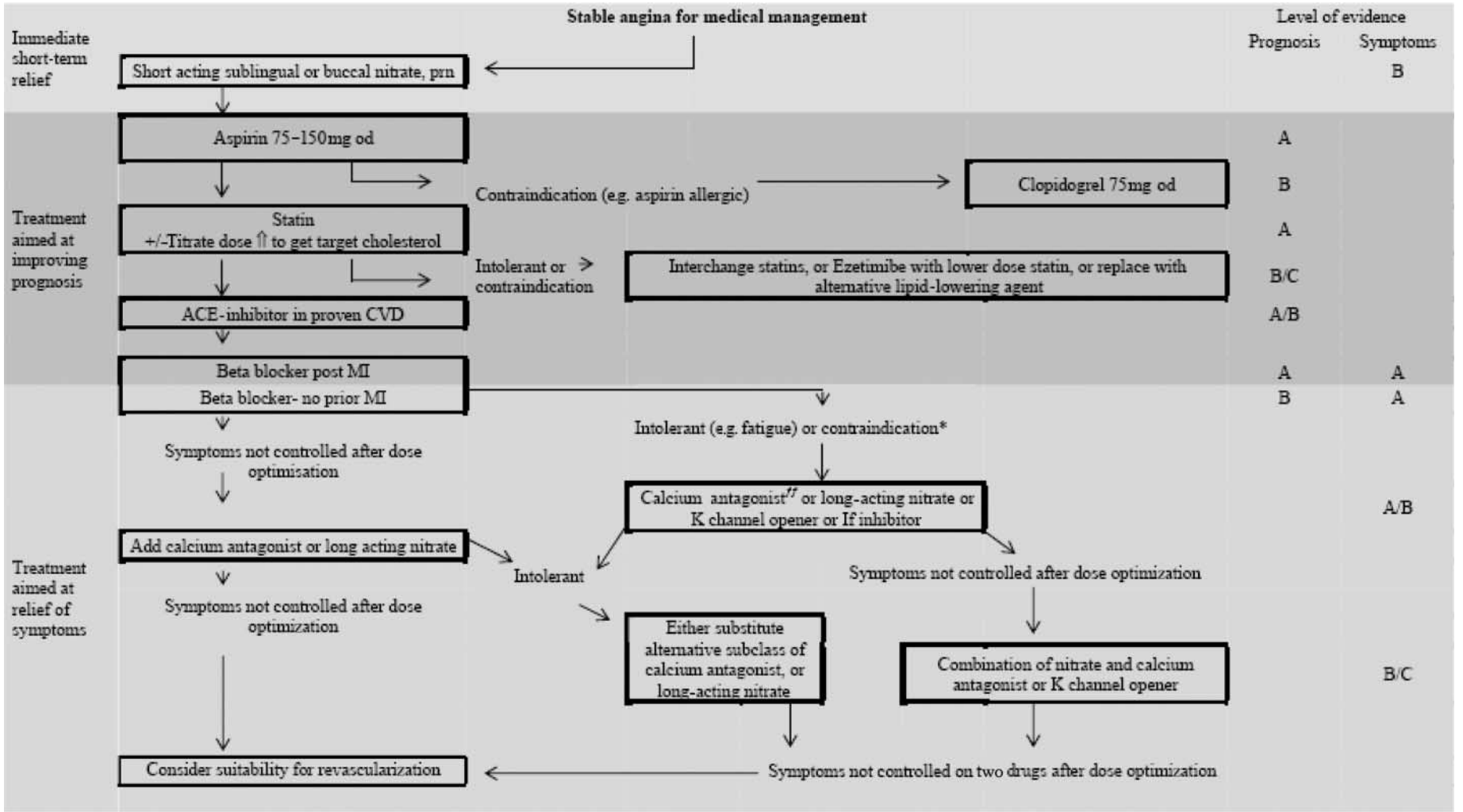

Figure 4 Algorithm for the medical management of stable angina. High-risk candidates for revascularization on prognostic grounds alone should be identified and referred appropriately. *Relative contraindications to beta-blockade include asthma, symptomatic peripheral vascular disease, and first degree heart block. ††Avoid short-acting dihydropyridine formulations when not combined with beta-blocker. Evidence for prognosis refers to evidence of reduction in CV death or CV death/MI. Evidence for symptoms includes reduction in the need for revascularization and hospitalization for chest pain.

on drug treatment. If vasospasm occurs in association with significant coronary disease, guideline recommendations for treatments to improve prognosis and secondary prevention should also be adhered to.

Recommendations for pharmacological therapy of vasospastic angina
Class I

(1) Treatment with calcium antagonists and if necessary nitrates in patients whose coronary arteriogram is normal or shows only non-obstructive lesions (level of evidence B)

Myocardial revascularization

There are two well-established approaches to revascularization for treatment of chronic stable angina caused by coronary atherosclerosis: surgical revascularization (CABG) and percutaneous coronary intervention (PCI). Currently both methods are facing rapid development with the introduction of minimally invasive and off-pump surgery and drug-eluting stents (DES). As in the case of pharmacological therapy the potential objectives of revascularization are two-fold, to improve survival or survival free of infarction, or to diminish or eradicate symptoms, and the individual risk of the patient as well as symptomatic status must be a major factor in the decision-making process.

Coronary artery bypass surgery

There are two main indications for CABG: prognostic and symptomatic. Prognostic benefit of CABG is mainly because of a reduction in cardiac mortality, as there is less evidence for reduction in myocardial infarction.[230,231] Evidence of prognostic benefit of CABG compared with medical therapy has not been demonstrated in low-risk patients (annual mortality $<1\%$).[231] In a meta-analysis of surgical trials comparing CABG with medical therapy, CABG was shown to improve prognosis in those at medium to high-risk, but even those in the medium risk had a 5 year mortality rate with medical therapy of 13.9%, annual mortality of 2.8%, which by contemporary standard appears high. Further observational data from the Duke registry confirmed that long-term mortality benefit associated with surgery was limited to high-risk groups.[232] Analyses of observational and randomized controlled trial data has revealed that the presence of specific coronary artery anatomy is associated with a better prognosis with surgery than with medical treatment.[104,231] Such disease includes.

(1) Significant stenosis of the left main (LM) stem
(2) Significant proximal stenosis of the three major coronary arteries
(3) Significant stenosis of two major coronary arteries, including high-grade stenosis of the proximal left anterior descending coronary artery

Significant stenosis was defined for these studies as $\geq 70\%$ of major coronary arteries or $\geq 50\%$ of the LM stem. The presence of impaired LV function increases the absolute prognostic advantage of surgery over medical treatment in all categories. This information comes from two major randomized studies; the European Coronary Artery study and the North American CASS study.[103,233]

Surgery has been convincingly shown to reduce symptoms and ischaemia, and to improve quality-of-life in patients with chronic angina. These effects are evident in a much wider range of subgroups than in which it has been shown to improve survival.[230] However, despite improvements over time, operative morbidity and mortality remain important considerations. Thus, individual risks and benefits should be discussed as thoroughly in low-risk patients in whom surgery is undertaken on symptomatic grounds alone, as in high-risk patients.

The overall operative mortality for CABG is between 1–4%,[9,234–237] depending on the population studied, and there are well-developed risk stratification models available for the assessment of risk in individual patients[238] Over the last 20 years the standard procedure has been to graft the left anterior descending artery (LAD) with the left internal thoracic artery (LITA) and use saphenous vein for the other bypass grafts. The recurrence of symptoms from vein graft disease remains a clinical problem. Large observational studies have shown that the use of the LITA graft improves survival and reduces the incidence of the late myocardial infarction, recurrent angina, and the need for further cardiac interventions.[239] Other arterial grafts which have been used include the radial artery and the right gastroepiploic artery. The greatest experience has been with the radial artery where reports have indicated patency rates of greater than 90% in the first 3 years of surgery.

The use of extra-corporeal circulation (cardiopulmonary bypass) to perform coronary artery surgery remains the most commonly used approach. But so-called 'off-pump' surgery may lead to a reduction in perioperative mortality and morbidity. Randomized trials comparing off-pump with the standard procedure are now available with no difference demonstrated in outcome in the first 1–3 years after surgery between off-pump and standard groups,[240,241] More recently, Khan *et al.*[242] in a further randomized trial with angiographic follow-up 3–6 months, showed a significant reduction in graft patency (90 vs. 98%) in the off-pump group. These studies suggest that the use of off-pump surgery is not a panacea but should be applied cautiously and selectively to patients with good target vessels and significant co-morbidity.

Percutaneous coronary intervention

Although percutaneous transluminal angioplasty was initially only used for the treatment of single vessel disease, advances in experience, equipment, particularly stents, and adjuvant therapy, have lead to a considerably expanded role for this modality of treatment in recent years. In patients with stable angina and suitable coronary anatomy, the use of stents and adequate adjuvant therapy allows a competent practitioner to perform either single or multivessel PCI with a high likelihood of initial procedural success and acceptable risk.[243] The risk of death associated with the procedure in routine angioplasty is $\sim$0.3–1%, with considerable variation possible. PCI may be considered an alternative to CABG for symptomatic relief of symptoms in almost all cases. On available evidence, PCI compared with medical therapy does not seem to provide substantial survival benefit in stable angina.[244]

Trial-based evidence indicates that PCI is more often effective than medical treatment in reducing events that impair quality-of-life (angina pectoris, dyspnoea, need for

re-hospitalization, or limitation of exercise capacity). The ACME investigators,[245] demonstrated superior control of symptoms and better exercise capacity in patients managed with PCI when compared with medical therapy. Death and MI were similar in both groups. However, mid-term results in patients with double-vessel disease did not demonstrate superior control of symptoms compared with medical therapy (similar improvement in exercise duration, freedom from angina, and improvement in quality-of-life at the time of 6-month follow-up) as was experienced by patients with single-vessel.[246] This small study ($n = 328$) suggests that PCI may be less effective in controlling symptoms in patients with double-vessel and stable angina when compared with single-vessel disease.

The RITA-2 trial[247] showed that PCI results in a better control of symptoms of ischaemia and improves exercise capacity compared with medical therapy, but is associated with a higher combined endpoint of death and periprocedural MI. In this trial, 1018 patients (62% with multivessel CAD and 34% with significant disease in the proximal segment of the left anterior descending coronary artery) with stable angina were randomized to PCI or medical therapy and followed for a mean of 2.7 years. Patients who had inadequate control of their symptoms with optimal medical therapy were allowed to cross-over to myocardial revascularization. AVERT[248] randomly assigned 341 patients with stable CAD, normal LV function, and Class I and/or II angina to PCI or medical therapy with 80 mg daily atorvastatin. At 18 months follow-up, 13% of the medically treated group had ischaemic events when compared with 21% of the PCI group ($P = 0.048$). Angina relief was greater in those treated with PCI. These data suggest that in low-risk patients with stable CAD, medical treatment including aggressive lipid-lowering therapy may be as effective as PCI in reducing ischaemic events. Greater improvement in anginal symptoms occurred with PCI.

Elective stent insertion and DES. In a meta-analysis of 29 trials involving 9918 patients, there was no evidence for a difference between routine coronary stenting and standard balloon angioplasty in terms of death or myocardial infarction or the need for CABG surgery. However, coronary stenting reduces the rate of restenosis and the need for repeat PCI,[249] findings confirmed in a further more recent meta-analysis.[250] However, in-stent restenosis remains a limitation in the efficacy of PCI for patients with stable coronary disease, with a need for target lesion revascularization between 5 and 25%.

DES have been the focus of attention of interventional coronary therapy after the RAVEL study.[251] Presently, three drugs have shown significantly positive effects in prospective randomized studies (Paclitaxel, Sirolimus, and its derivative Everolimus). To date randomized trials include only patients with single-vessel disease, and with stable or unstable angina. The use of drug eluting stents shows a consistently better treatment effect compared to bare metal stents, reducing the risk of restenosis and major adverse cardiac events including target vessel revascularization. Reported incidence of major adverse cardiac events (MACE) over 9 months range between 7.1 and 10.3% with DES stents compared with a range between 13.3 and 18.9. More specific guidelines on the use of DES are available in the ESC guidelines on PCI.[252]

Revascularization vs. medical therapy

Aside from studies dealing exclusively with the effects of either PCI vs. medical therapy or surgery vs. medical therapy, several hybrid studies have investigated the effects of revascularization (either PCI or surgery) compared with medical therapy. The Asymptomatic Cardiac Ischaemia Pilot[253] study provides additional information comparing medical therapy with PCI or CABG revascularization in patients with documented CAD and asymptomatic ischaemia by both stress-testing and ambulatory ECG monitoring. This small study ($n = 558$) randomized patients with minimal symptoms but evidence of ischaemia on testing, who were suitable for revascularization by PCI or CABG, to one of three treatment strategies: angina-guided drug therapy, angina plus ischaemia-guided drug therapy, and revascularization by PCI or CABG surgery. At 2 years of follow-up, death or MI had occurred in 4.7% of the revascularization patients when compared with 8.8% of the ischaemia-guided group and 12.1% of the angina-guided group ($P < 0.01$ for the revascularized group compared with ischaemia- or angina-guided groups). The results of the ACIP trial indicate that higher-risk patients who are asymptomatic or have minimal symptoms but demonstrable ischaemia and significant CAD may have a better outcome with revascularization with either CABG or PCI compared with those managed medically.

A Swiss study (TIME),[254] in elderly patients (mean age 80 years) with severe angina randomized participants to immediate invasive or continued medical therapy. Of those randomized to invasive therapy, 52% received PCI and 21% had CABG. Invasive therapy was associated with a statistically significant improvement in symptoms at 6 months, but the difference was not maintained at 1 year, partly because of a 48% delayed revascularization rate in the medically treated arm. Death and MI were not significantly different between the two treatment strategies. Investigators in the Medicine, Angioplasty or Surgery Study (MASS)[255] randomized patients with stable angina and isolated disease of the left descending coronary artery to medical treatment or PCI (including stenting) or CABG using a combined endpoint of cardiac death, MI, or refractory angina requiring repeat revascularization by surgery. At 3 years of follow-up, this combined endpoint occurred in 24% of PCI patients, in 17% of medical patients, and in 3% of surgical patients. Importantly, there was no significant difference in overall survival in the three groups. Death or MI occurred in 1% of the CABG group, 2% of the PCI group, and 1.4% of the medically treated group.

PCI vs. surgery

A large number of clinical trials have compared PCI with surgery in order to establish the choice of revascularization technique, both before and subsequent to the introduction of stenting,[236,256,257] and in multivessel as well as single vessel disease. Meta-analysis of trials conducted before 1995,[258] when coronary stenting was rare, revealed no significant differences in the treatment strategies for either death or the combined endpoint of death or MI. Mortality during the initial hospitalization for the procedure occurred in 1.3% of the CABG group and 1% of the PCI group. The need for subsequent revascularization was significantly higher in the PCI group, and although patients were significantly less likely to have angina 1 year after bypass surgery than

after PCI, by 3 years this difference was no longer statistically significant. Results from the BARI study, the largest single randomized trial of PCI vs. surgery, not included in this meta-analysis, were nonetheless consistent with these findings, although a survival advantage with bypass surgery was observed in the diabetic subgroup.[259]

More recent trials, such as the ARTS[260] and SOS trials,[256] have incorporated the use of stents as part of PCI. The ARTS 1 trial[260] compared the strategy of multiple stent implantation with the aim of complete revascularization vs. bypass surgery in patients with multivessel disease (MVD). However, this trial was not exclusively among patients with stable angina; 37% and 35% respectively, in both arms had unstable angina, 57% and 60% respectively, had stable angina, 6% and 5% respectively, had silent ischaemia. One year after the procedure, coronary stenting for MVD in selected patients offered a similar outcome in terms of death, stroke, and myocardial infarction as bypass surgery. However, stenting was associated with a greater need for repeated revascularization.

A meta-analysis including trials of stents[234] suggests a mortality benefit with CABG compared with PCI at 5 years which continued to 8 years in patients with MVD, as well as significantly less angina and less need for repeat revascularization. Subgroup analysis of trials with and without stents indicated significant heterogeneity between the two groups, with trials performed pre-stents showing a trend towards reduced mortality favouring CABG which was not evident in the trials with stents. A more recent meta-analysis of four randomized controlled trials of PCI with stents compared with bypass surgery ($n = 3051$) showed no significant difference between the treatment strategies in the primary endpoint of death, MI, or stroke at 1 year. However, observational data with 3 year follow-up on $>60\,000$ patients from the New York Cardiac Registry indicated that for patients with two or more diseased coronary arteries, CABG was associated with higher adjusted rates of long-term survival than stenting.

To summarize, the trial evidence suggests that, outside of the population with high-risk indicators, which have been proven to benefit prognostically from surgery, either PCI or surgery may be considered as an effective option for the treatment of symptoms. After an initial pharmacological approach, revascularization may be recommended for patients with suitable anatomy who do not respond adequately to medical therapy, or for the individual patient who, regardless of age, wishes to remain physically active (performing regular physical exercise).

In non-diabetic patients with one to two vessel disease without high grade stenosis of the proximal LAD in whom angioplasty of one or more lesions has a high likelihood of initial success, PCI is generally the preferred initial approach, influenced by factors such as the less invasive nature and lower initial risk of the initial procedure, and the absence of survival advantage of CABG in lower risk subgroups. The individual circumstances and preferences of each patient must be considered carefully when planning the treatment strategy.

In asymptomatic patients, revascularization cannot improve symptoms and the only appropriate indication for revascularization with PCI would be to reduce the likelihood of ischaemic complications in the future. Evidence to support this strategy is limited only to those patients with objective evidence of extensive ischaemia in whom revascularization (either PCI or CABG) may reduce the likelihood of mortality relative to an angina-guided strategy (ACIP).[253] PCI may be considered for mildly symptomatic patients in the category of higher-risk ischaemia and severe anatomic CAD only if there is a high likelihood of success and a low risk of morbidity or mortality.

Specific patient and lesion subsets

Patients with severely depressed LV function and/or high surgical risk, patients with LM disease, patients with diabetes and MVD, and patients with previous bypass surgery warrant particular consideration when selecting revascularization options.

Patients in whom surgical risk is prohibitively high may benefit from revascularization by PCI, particularly when residual viability can be demonstrated in the dysfunctioning myocardium perfused by the target vessel(s). This issue is currently addressed in two large randomized studies, the STICH,[261] and the HEART UK[262] trials.

Although PCI in LM stem disease is feasible, and good results have been achieved in registries comparing DES and bare metal stents[263] surgery should remain the preferred approach until the outcome of further trials are known.

Subgroup analyses of randomized trials have shown reduced mortality with bypass surgery compared with PCI in diabetic patients with MVD.[264,265] The BARI trial was the largest of these trials, and the only one in which a statistical difference in mortality was detected between the treatment groups in the diabetics.[259,266] A limitation of these trials is that they were conducted before the widespread use of DES stents or adjuvant peri-procedural antiplatelet therapy. Two major trials are underway to address this important issue, BARI 2 Diabetes (BARI 2D), and FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus). However, for the present, due consideration should be given to the evidence available and PCI should be used with reservation in diabetics with MVD until the results of further trials are known.

There are no randomized controlled trials comparing treatment options in patients with previous bypass surgery. Redo surgery may be undertaken on symptomatic grounds where the anatomy is suitable. However, the operative risk of re-do bypass surgery is as high as three-fold greater than initial surgery, and for those with a patent ITA grafts there is the additional risk of damage to this graft during surgery.

On the other hand PCI can be performed following previous surgical revascularization, either in the vein graft or arterial graft, or the native coronary tree beyond the graft which is not revascularized, and may provide a useful alternative to redo surgery for symptomatic relief.

Finally the case of a chronic total occlusion which cannot be crossed, in patients with MVD, failure to treat chronic total occlusions will result in incomplete revascularization, which could be avoided when the patient is referred for bypass surgery.

Indications for revascularization

In general, patients who have indications for coronary arteriography and in whom catheterization reveals severe coronary artery stenosis are also potential candidates for myocardial revascularization. In addition, a patient is potentially eligible for revascularization if:

(1) Medical therapy is unsuccessful in controlling symptoms to the patient's satisfaction
(2) Non-invasive tests reveal a substantial area of myocardium at risk
(3) There is a high likelihood of success and acceptable risk of morbidity and mortality
(4) The patient prefers an interventional rather than a medical approach and is fully informed of the risks of this route of therapy in their individual case

An adequate response to therapy must be judged in consultation with the patient. For some, Class I symptoms (angina only on strenuous exertion but not during ordinary activity) are acceptable, but others may wish for complete abolition of their symptoms. Recommendations for revascularization on symptomatic grounds, as summarized in *Table 6* or below, have taken into account the range of symptomatic grades for which evidence is available and should be construed in this fashion rather than as a directive to perform revascularization across the entire range of symtomatology. What is an acceptable risk of morbidity and mortality should also be considered on an individual basis for each patient. Ideally patients should not be advised to have a procedure for which the procedural mortality exceeds their estimated annual mortality unless there is evidence of substantial prognostic benefit in the longer term, or symptoms are having a serious impact on their quality-of-life despite appropriate medical therapy.

Selection of the method of revascularization should be based on:

(1) Risk of periprocedural morbidity and morbidity
(2) Likelihood of success, including factors such as technical suitability of lesions for angioplasty or surgical bypass
(3) Risk of restenosis or graft occlusion
(4) Completeness of revascularization. If considering PCI for MVD, is there a high probability that PCI will provide complete revascularization or at least in the same range as CABG?
(5) Diabetic status
(6) Local hospital experience in cardiac surgery and interventional cardiology
(7) Patient's preference

Contraindications to myocardial revascularization comprise:

(1) Patients with one or two vessel CAD without significant proximal LAD stenosis who have mild or no symptoms and have not received an adequate trial of medical therapy or have no demonstrable ischaemia or only a limited area of ischaemia/viability on non-invasive testing
(2) Borderline (50–70%) coronary stenosis in location other than LM and no demonstrable ischaemia on non-invasive testing
(3) Non-significant (<50%) coronary stenosis
(4) High risk of procedure-related morbidity or mortality (>10–15% mortality risk) unless the risk of the procedure is balanced by an expected significant improvement in survival or the patient's quality-of-life without the procedure is extremely poor

Constant rapid developments in PCI and CABG, as well as significant progress in medical treatment and secondary prevention of stable angina, have generated the need for large randomized trials comparing different treatment strategies in selected groups of patients. Many questions in the management of stable angina remain incompletely answered, and further questions are generated by the development of new treatment modalities, necessitating the constant revision and updating of these guidelines and a need for practising clinicians to remain abreast of current literature in the area in the interim.

Recommendations for revascularization to improve prognosis in patients with stable angina
Class I

(1) CABG for significant LM CAD or its equivalent (i.e. severe stenosis of ostial/proximal segment of left descending and circumflex coronary arteries) (level of evidence A)
(2) CABG for significant proximal stenosis of three major vessels, particularly in those patients with abnormal LV function, or with early or extensive reversible ischaemia on functional testing (level of evidence A)
(3) CABG for single or two vessel disease with high grade stenosis of proximal LAD with reversible ischaemia on non-invasive testing (level of evidence A)
(4) CABG for significant disease with impaired LV function and viability demonstrated by non-invasive testing (level of evidence B)

Class IIa

(1) CABG for single- or two-vessel CAD without significant proximal LAD stenosis in patients who have survived sudden cardiac death or sustained ventricular tachycardia (level of evidence B)
(2) CABG for significant three vessel disease in diabetics with reversible ischaemia on functional testing (level of evidence C)
(3) PCI or CABG for patients with reversible ischaemia on functional testing and evidence of frequent episodes of ischaemia during daily activities (level of evidence C)

Recommendations for revascularization to improve symptoms in patients with stable angina
Class I

(1) CABG for MVD technically suitable for surgical revascularization in patients with moderate to severe symptoms not controlled by medical therapy, in whom risks of surgery do not outweigh potential benefits (level of evidence A)
(2) PCI for single vessel disease technically suitable for percutaneous revascularization in patients with moderate to severe symptoms not controlled by medical therapy, in whom procedural risks do not outweigh potential benefits (level of evidence A)
(3) PCI for MVD without high risk coronary anatomy, technically suitable for percutaneous revascularization in patients with moderate to severe symptoms not controlled by medical therapy and in whom procedural risks do not outweigh potential benefits (level of evidence A)

Class IIa

(1) PCI for single vessel disease technically suitable for percutaneous revascularization in patients with mild to

moderate symptoms which are nonetheless unacceptable to the patient, in whom procedural risks do not outweigh potential benefits (level of evidence A)
(2) CABG for single vessel disease technically suitable for surgical revascularization in patients with moderate to severe symptoms not controlled by medical therapy, in whom operative risk does not outweigh potential benefit (level of evidence A)
(3) CABG in MVD technically suitable for surgical revascularization in patients with mild to moderate symptoms, which are nonetheless unacceptable to the patient, in whom operative risk does not outweigh potential benefit (level of evidence A)
(4) PCI for MVD technically suitable for percutaneous revascularization in patients with mild to moderate symptoms, which are nonetheless unacceptable to the patient, in whom procedural risks do not outweigh potential benefits (level of evidence A)

Class IIb

(1) CABG in single vessel disease technically suitable for surgical revascularization in patients with mild to moderate symptoms, which are nonetheless unacceptable to the patient, in whom operative risk is not greater than estimated annual mortality (level of evidence B)

Special subgroups

Women

The evaluation of chest pain in women is less straightforward than in men at multiple levels, because of gender differences in presentation and disease manifestation[267] and also the preponderance of male-specific data in the published literature.

There are numerous differences in the epidemiology and primary manifestation of coronary heart disease (CHD) in women and men. Stable angina is the most frequent initial manifestation of CHD in women, but MI or sudden death the most frequent initial manifestation in men.[3,268,269] Also, although the incidence of CHD death or MI is greater in men than in women at all ages, the incidence of angina in women, while lower in younger decades, exceeds that of men in the post-menopausal age groups. Therefore, it is not surprising that at population level, some studies report an even higher prevalence of Rose questionnaire angina in middle-aged and elderly women than in men of comparable age.[270–274] However, in population-based studies, the incidence of fatal CHD is higher in men with angina than in women with angina, possibly partly due to misclassification of angina as CHD in a proportion of women.

The diagnosis of angina in women is more difficult than in men for several reasons. Atypical symptoms are more common in women, but this is 'atypical' compared with the typical symptoms described by men. Patient perception of pain, and the language used to report symptoms are different between men and women.[275]

To compound the problem the correlation between symptoms and 'significant' luminal obstruction at coronary angiography is weaker in women than in men. In the Coronary Artery Surgery Study[276] 62% of women with typical angina had significant coronary stenoses when compared with 40% of women with atypical angina and 4% of women with non-ischaemic pain, illustrating the lower prevalence of angiographically verified CHD in women than in men for all forms of chest pain, including typical and atypical angina as well as non-cardiac chest pain.

When used for the detection of significant coronary disease, exercise ECG testing has a higher false-positive rate in women (38–67%) than men (7–44%)[277]—largely because of the lower pretest likelihood of disease[31]—but a lower false-negative rate in women.[278] This results in a high negative predictive value, signifying that a negative result of non-invasive testing reliably excludes the presence of CAD. The difficulties of using exercise testing for diagnosing obstructive CAD in women have led to speculation that stress imaging may be preferred over standard stress testing. Myocardial perfusion scintigraphy or echocardiography could be a logical addition to treadmill testing in this circumstance. However, the sensitivity of thallium perfusion scans may be lower in women than in men.[279] Artifacts due to breast attenuation, usually manifest in the anterior wall, can be an important caveat in the interpretation of women's perfusion scans. Similarly, exercise or pharmacologic stress echocardiography may help avoid artifacts specifically due to breast attenuation. Indeed, numerous studies have indicated the value of stress echocardiography as an independent predictor of cardiac events in women with known or suspected CAD.[45,280,281]

Despite its limitations in women, routine exercise ECG testing has been shown to reduce procedures without loss of diagnostic accuracy. Indeed, only 30% of women (in whom a reasonably certain diagnosis of CAD could not be reached or excluded) need be referred for further testing.[282] Although the optimal strategy for diagnosing obstructive CAD in women remains to be defined, the Task Force believes that there are currently insufficient data to justify replacing standard exercise testing with stress imaging in all women being evaluated for CAD. In many women with a low pretest likelihood of disease, a negative exercise test result will be sufficient, and imaging procedures will not be required.[282]

It is important to emphasize that women with objective evidence of moderate to severe ischaemia at non-invasive testing should have equal access to coronary arteriography as men. Furthermore, limited female representation in clinical trials of secondary prevention to date is not a justification to apply guidelines differently to men and women after CAD is diagnosed.

It is known that women have a higher morbidity and mortality after suffering myocardial infarction than men, and it has been suggested by some that less vigorous treatment in women may impact on reduced survival in women after myocardial infarction.[283] A review of 27 studies concluded that the reasons for increased early mortality among women were older age and presence of other unfavourable baseline clinical characteristics.[284] Subsequent investigation found an interaction between gender and age, with a female excess of mortality in younger patients (<50 years of age) that diminishes with age.[285]

Reports of the impact of gender on utilization of investigations and therapies and on subsequent clinical outcome in stable settings are similarly divergent. In a recent Dutch study, 1894 patients (1526 men, 368 women) with angiographically documented CAD were evaluated over a 16-year period (1981–1997). Over time, the number of angioplasty procedures increased significantly from 11.6–23.2% for

men, and for women from 17.6–28.0%, whereas the number of coronary artery bypass procedures decreased in men from 34.9% to 29.5% and in women from 42.6–30.6%.[286] However, interpretation of this and other coronary arteriography registries are limited by their intrinsic referral bias. Data from the Euro Heart Survey of Stable Angina conducted in 2003 suggests significant bias exists against the use, not just of arteriography, but also of exercise testing in women, even after adjustment for factors such as age, comorbidity, severity of symptoms, and in the case of arteriography, results of non-invasive testing.[287] In the same study women were less likely to receive revascularization and were less likely to receive effective secondary preventive medical therapy. Such findings suggest that the perceived difficulties in diagnosis and limited female-specific literature regarding the treatment of angina, along perhaps with more complex social issues, have perpetuated the situation where women with stable angina often remain under-investigated and under-treated.

Diabetes mellitus

Both insulin-dependent diabetes mellitus (type 1) and non-insulin-dependent diabetes mellitus (type 2) are associated with an increased risk of CVD. Furthermore, coronary heart disease (CHD) mortality is increased three-fold in diabetic men and two- to five-fold in diabetic women, compared with age- and sex-matched non-diabetic persons[288] Moreover, a number of epidemiological reports indicate that in patients with diabetes, the higher the blood glucose, the greater the incidence of CVD,[289,290]

The clinical manifestations of CHD in diabetic subjects are similar to those in non-diabetic patients, with angina, MI, and heart failure being the most prominent, but the symptoms tend to occur at an earlier age in diabetic patients. It is generally accepted that the prevalence of asymptomatic ischaemia is increased in patients with diabetes. However, because of considerable variation in inclusion and exclusion criteria as well as screening tests in studies to date, it is somewhat difficult to estimate the increased frequency of silent ischaemia accurately.[291]

There is growing interest in the use of myocardial perfusion scanning and other techniques to detect ischaemia in asymptomatic diabetic individuals.[292] There is also data to suggest that individuals with diabetes may have subclinical ventricular dysfunction, which negatively impacts on exercise capacity,[293] an important endpoint of exercise testing, but the impact of this finding on the diagnostic and prognostic information yielded by conventional testing in a symptomatic population is not clear. Thus the cardiac assessment of symptomatic ischaemia in diabetic patients should, in general, parallel that in non-diabetic subjects, with similar indications for exercise testing, myocardial perfusion test, and coronary arteriography. As CVD accounts for 80% of mortality in patients with diabetes mellitus,[294] emphasis should be placed on early diagnosis and aggressive treatment in this population.

Current strategies for optimal care of patients with diabetes mellitus include vigorous and persistent efforts to achieve physiologic control of blood glucose and control of other risk factors such as dyslipidaemia, hypertension, renal disease, obesity, and smoking. Abundant evidence is now available that long-term maintenance of near-normal blood glucose levels is protective of patients with diabetes and substantially reduces complications and mortality in both diabetes type 1 and 2.[295]

Conventional therapies for CHD with nitrates, beta-blockers, calcium channel blockers, statins, antiplatelets agents, and coronary revascularization procedures have similar indications in diabetic and non-diabetic patients. In addition, ACE-inhibitors are indicated in diabetic patients with proven vascular disease.[75] The relative merits of PCI and CABG in diabetic patients are discussed in the section on revascularization. Unfortunately, owing to the chronic metabolic disturbances of diabetes mellitus, these patients usually have a continuous progression of native atherosclerotic disease, leading to an extensive CHD with high rates of MVD and of restenosis. Thus, even after successful invasive procedures, good management of CVD risk factors and a tight glycaemic control are essential for good long-term outcome.[296]

The elderly

After the age of 75 years there is an equal prevalence of CAD in men and women.[297] The disease is more likely to be diffuse and severe; LM coronary artery stenosis and triple vessel disease are more prevalent in older patients, as is impaired LV function. The evaluation of chest pain syndromes in the elderly can be difficult because complaints of chest discomfort, weakness, and dyspnoea are common, and co-morbid conditions that mimic angina pectoris are frequently present. Reduced activity levels and blunted appreciation of ischaemic symptoms become the norm with advancing age.[298] In large community studies of men and women $>$65-years old, those with atypical symptoms and typical angina were shown to have a similar 3 year cardiac mortality rates.[299] The performance of exercise testing poses additional problems in the elderly. Functional capacity often is compromised from muscle weakness and deconditioning. More attention must be given to the mechanical hazards of exercise, and less challenging protocols may be more appropriate. Arrhythmias also occur more frequently with increasing age. The higher prevalence of disease means that more exercise test results are false-negative.[300] False-positive test results also are more frequent because of the higher prevalence of confounders such as prior MI, LVH from valvular diseases, hypertension, and conduction disturbances. Despite these differences, exercise testing remains important also in the elderly. The Task Force believes that exercise electrocardiographic testing should remain the initial test in evaluating elderly patients with suspected CAD unless the patient cannot exercise, in which case it may be replaced by pharmacological stress imaging.

It is important to emphasize that elderly patients with objective evidence of moderate to severe ischaemia at non-invasive testing should have similar access to coronary arteriography as younger patients. Notably, diagnostic coronary arteriography has relatively little increased risk (compared with younger patients) in older patients undergoing elective evaluation.[70] However, age $>$75 years is an important predictor of contrast-induced nephropathy.[301]

Medical treatment is more complex in elderly patients. Indeed, changes in drug bioavailability, elimination, and sensitivity mean that dose modification is essential when prescribing cardiovascular drugs to elderly patients.[302] Further issues which should be taken into account when

prescribing for the elderly include risk of drug interactions, polypharmacy, and compliance problems. Nevertheless, in this patient population anti-anginal medications are as efficacious in reducing symptoms and statins in improving prognosis[160] as they are in young patients. Considering symptoms as well as prognosis, elderly patients have the same benefit from medical therapy, angioplasty, and bypass surgery as younger patients.[303–305]

Chronic refractory angina

Drugs and revascularization procedures, i.e. CABG and percutaneous transluminal angioplasty, can adequately manage the majority of patients suffering from ischaemic heart disease. However, there are patients who remain severely disabled by angina pectoris in spite of different forms of conventional treatment. The problem of chronic refractory angina was addressed in a Report from the ESC Joint Study Group on the Treatment of Refractory Angina, published in 2002.[306]

Chronic stable refractory angina can be defined as a clinical diagnosis based on the presence of symptoms of stable angina, thought to be caused by ischaemia due to advanced coronary disease and which are not controllable by a combination of maximal medical therapy, bypass surgery, and percutaneous intervention. Non-cardiac causes of chest pain should be excluded, and where appropriate, cognitive behavioural therapy, psychological assessment, and/or psychiatric consultation may be considered.

Chronic refractory angina requires an effective optimization of medical treatment assuring the use of different drugs in maximal tolerated doses. This issue is extensively developed in the original document of the Joint Study Group. Within the last few years new modalities exploring new concepts of therapy are under extensive evaluation, not all have been proven successful.

- Neuromodulation techniques (transcutaneous electric nerve stimulation and spinal cord stimulation)
- Thoracic epidural anaesthesia
- Endoscopic thoracic sympathectomy
- Stellate ganglion blockade
- Transmyocardial or percutaneous laser
- Angiogenesis
- Enhanced external counterpulsation (EECP)
- Heart transplantation
- Drugs that modulate metabolism

Transcutaneous electrical stimulation and spinal cord stimulation are well established methods used in several centres for the management of refractory angina with positive effects on symptoms and a favourable side-effect profile.[307–309] These techniques have a favourable analgesic effect even without any improvement in myocardial ischaemia. A significant increase in the average exercise time on treadmill testing has however been observed. The number of published reports and the number of patients enrolled in clinical trials are small and the long-term effects of these techniques are unknown.

EECP is an interesting non-pharmacologic technique which has also been investigated. The technique is well tolerated when used over a period of 35 h of active counterpulsation during 4–7-week period. Anginal symptoms were improved in ~75–80% of patients.

Transmyocardial laser revascularization has been compared with medical therapy in several studies. In one study (in 275 patients with CCS Class IV symptoms), 76% of patients who had undergone transmyocardial laser improved two or more functional classes after 1 year of follow-up, as compared with 32% ($P < 0.001$) of the patients who received medical therapy alone.[310] Mortality did not differ significantly between the two groups. However, further studies of transmyocardial revascularization (either surgically or percutaneously) have been unable to confirm this benefit.[311,312]

Conclusions and recommendations

(1) Angina pectoris due to coronary atherosclerosis is a common and disabling disorder. Although compatible with longevity, there is an increased risk of progression to MI and/or death. With proper management, the symptoms can usually be controlled and the prognosis substantially improved

(2) Every patient with suspected stable angina requires prompt and appropriate cardiological investigation to ensure that the diagnosis is correct and that the prognosis is evaluated. As a minimum, each patient should have a carefully taken history and physical examination, a comprehensive risk factor evaluation and a resting electrocardiogram

(3) To confirm the diagnosis and plan further management an initial non-invasive strategy, using exercise ECG, stress echo, or myocardial perfusion scintigraphy is most appropriate. This allows an assessment of the likelihood and the severity of CHD in patients with mild to moderate symptoms, and effective risk stratification. In many patients coronary arteriography may follow, but an initial invasive strategy without prior functional testing is rarely indicated, and may only be considered for patients with new onset severe or uncontrolled symptoms

(4) The exercise ECG should be interpreted with attention to haemodynamic response, workload achieved, and clinical features of the individual as well as symptoms and ST-segment response. Alternative investigations are needed when exercise ECG is not possible or interpretable, or in addition to exercise testing when the diagnosis remains uncertain or functional assessment is inadequate

(5) In addition to their role in intial assessment of stable angina symptoms, myocardial perfusion scintigraphy and stress echocardiography are of particular value in demonstrating the extent and localization of myocardial ischaemia

(6) Echocardiography and other non-invasive imaging modalities, such as magnetic resonance imaging are helpful in evaluating ventricular function

(7) The interpretation of chest pain is particularly difficult in young-and middle-aged women. The classical symptom complex of chronic stable angina, which is a reliable indicator of obstructive coronary disease in men is not so in younger women. This problem is compounded by the higher prevalence of coronary artery spasm and 'Syndrome X' in women with chest pain, and by the frequency of 'false positive' exercise tests. However,these complexities should not prevent

appropriate investigation and treatment of women, particularly the use of non-invasive investigations for the puposes of risk stratification, and use of secondary preventative therapies

(8) After initial risk evaluation, risk factor correction by life-style modification should be implemented in addition to pharmacological intervention as necessary. Strict diabetic control and weight control along with smoking cessation strategies are strongly advised in all patients with coronary disease, and blood pressure control is extremely important. Successful risk factor management may modify the initial risk assessment

(9) In terms of specific pharmacological therapy, short acting nitrates, when tolerated, may be used to provide acute symtomatic relief. In the absence of contraindications or intolerance, patients with stable angina pectoris should be treated with aspirin (75 mg/day) and statin therapy. A beta-blocker should be used first line, or alternatively a calcium channel blocker or long acting nitrate may be used to provide anti-anginal effects, as described earlier, with additional therapy as necessary. ACE-inhibition is indicated in patients with co-existing ventricular dysfunction, hypertension or diabetes, and should be considered in patients with other high-risk features. Beta-blockers should be recommended in all post-MI patients and in patients with LV dysfunction, unless contraindicated

(10) Anti-anginal drug treatment should be tailored to the needs of the individual patient, and should be monitored individually. The dosing of one drug should be optimized before adding another one, and it is adviseable to switch drug combinations before attempting a three drug regimen

(11) If not undertaken for further prognostic evaluation, coronary arteriography should be undertaken when symptoms are not satisfactorily controlled by medical means, with a view to revascularization

(12) PCI is an effective treatment for stable angina pectoris, and is indicated for patients with angina not satisfactorily controlled by medical treatment when there are anatomically suitable lesions. Restenosis continues to be a problem, which has been diminished by advances in stenting technology. There is no evidence that PCI reduces the risk of death in patients with stable angina compared with medical or surgical therapy

(13) CABG is highly effective in relieving the symptoms of stable angina and reduces the risk of death over long-term follow-up in particular subgroups of patients, such as those with LM stem stenosis, proximal LAD stenosis, and three vessel disease, especially if LV function is impaired

(14) There is evidence that some gaps remain between best practice and usual care in the management of stable angina. Specifically, many individuals with stable angina are not referred for functional testing to confirm the diagnosis and determine prognosis. Furthermore, there is variability in rates of prescription of statins and aspirin. Because of the wide variations in the quality of care afforded to sufferers from angina, there is a strong case for auditing several components of the management of the condition. As is the practice in some countries, local, regional, or national registers of the outcome of PCI and surgery should be created and maintained

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