



# Guidelines on the management of stable angina pectoris: full text<sup>†</sup>

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

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### Table of Contents

Preamble . . . . .	2	Echocardiography at rest . . . . .	13
Introduction . . . . .	3	Ambulatory ECG monitoring . . . . .	13
Definition and pathophysiology . . . . .	3	Non-invasive techniques to assess coronary calcification and coronary anatomy . . . . .	14
Epidemiology . . . . .	5	Invasive techniques to assess coronary anatomy . . . . .	14
Natural history and prognosis . . . . .	5	Coronary arteriography . . . . .	14
Diagnosis and assessment . . . . .	6	Intravascular ultrasound . . . . .	14
Symptoms and signs . . . . .	6	Invasive assessment of functional severity of coronary lesions . . . . .	15
Laboratory tests . . . . .	7	Risk stratification . . . . .	15
Chest X-ray . . . . .	8	Risk stratification using clinical evaluation . . . . .	16
Non-invasive cardiac investigations . . . . .	8	Risk stratification using stress testing . . . . .	19
Resting ECG . . . . .	8	Risk stratification using ventricular function . . . . .	20
ECG stress testing . . . . .	9	Risk stratification using coronary arteriography . . . . .	22
Stress testing in combination with imaging . . . . .	11		

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Special diagnostic considerations: angina with 'normal' coronary arteries . . . . .	22
Syndrome X . . . . .	23
Vasospastic/variant angina . . . . .	24
Treatment . . . . .	25
Aims of treatment . . . . .	25
General management . . . . .	25
Treatment of the acute attack . . . . .	25
Smoking . . . . .	25
Diet and alcohol . . . . .	25
Omega-3 fatty acids . . . . .	25
Vitamins and antioxidants . . . . .	26
Hypertension, diabetes, and other disorders . . . . .	26
Physical activity . . . . .	26
Psychological factors . . . . .	26
Car driving . . . . .	26
Sexual intercourse . . . . .	26
Employment . . . . .	26
Pharmacological treatment of stable angina pectoris . . . . .	26
Pharmacological therapy to improve prognosis . . . . .	27
Pharmacological treatment of symptoms and ischaemia . . . . .	34
Special therapeutic considerations: cardiac Syndrome X and vasospastic angina . . . . .	37
Myocardial revascularization . . . . .	38
Coronary artery bypass surgery . . . . .	38
Percutaneous coronary intervention . . . . .	39
Revascularization vs. medical therapy . . . . .	39
PCI vs. surgery . . . . .	40
Specific patient and lesion subsets . . . . .	41
Indications for revascularization . . . . .	41
Treatment of stable angina: multi-targeted treatment of a multi-faceted disease . . . . .	43
Special subgroups . . . . .	43
Women . . . . .	43
Diabetes mellitus . . . . .	44
Elderly . . . . .	45
Chronic refractory angina . . . . .	45
Conclusions and Recommendations . . . . .	46
References . . . . .	47

## Preamble

Guidelines and Expert Consensus documents aim to present management recommendations based on all of the relevant evidence 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, taking into account the impact on outcome and 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 mind of physicians. In order to avoid these pitfalls, the ESC

and other organizations have issued recommendations for formulating and issuing Guidelines and Expert Consensus Documents. The ESC recommendations for guidelines production can be found on the ESC website (Recommendations for ESC Guidelines Production at [www.escardio.org](http://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 management and/or prevention of a given condition. Estimates of the expected health outcomes are included, where data exist. The strength of evidence for or against particular procedures or treatments is weighed, according to predefined 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 practice, by describing the range of generally acceptable approaches to diagnosis and treatment. However, the ultimate judgment regarding the care of individual patients must be made by the physician in charge of their care.

The ESC Committee for Practice Guidelines (CPG) supervises and coordinates the preparation of new Guidelines and Expert Consensus Documents produced by 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 do not put them into practice. Implementation programmes are thus necessary and form an important component of the dissemination of 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.

All in all, 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 implementation programmes for the recommendations. The loop between clinical research, writing of guidelines, and implementing them into clinical practice can then 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

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

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, and registries

## Introduction

Stable angina pectoris is a common and disabling disorder. However, the management of stable angina has not been subjected to the same scrutiny by large randomized trials as has, for example, that of acute coronary syndromes (ACS) including unstable angina and myocardial infarction (MI). The optimal strategy of investigation and treatment is difficult to define, and the development of new tools for the diagnostic and prognostic assessment of patients, along with the continually evolving evidence base for various treatment strategies, mandates that the existing guidelines be revised and updated. The Task Force has therefore 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, namely myocardial ischaemia due to coronary artery disease (CAD), usually macrovascular, i.e. involving large coronary arteries, 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<sup>1</sup> 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 *Table 1*.

## 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. William Heberden first introduced the term 'angina pectoris' in 1772<sup>2</sup> to characterize a syndrome in which there was 'a sense of strangling and anxiety' in the chest, especially associated with exercise, although its pathological aetiology was not recognized until some years later.<sup>3</sup> It is now usual to confine the term to 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 in the absence of 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.

Myocardial ischaemia is caused by an imbalance between myocardial oxygen supply and myocardial oxygen consumption. Myocardial oxygen supply is determined by arterial oxygen saturation and myocardial oxygen extraction, which are relatively fixed under normal circumstances, and coronary flow, which is dependent on the luminal cross-sectional area of the coronary artery and coronary arteriolar tone. Both cross-sectional area and arteriolar tone may be dramatically altered by the presence of atherosclerotic plaque within the vessel wall, leading to imbalance between supply and demand when myocardial oxygen demands increase, as during exertion, related to increases in heart rate, myocardial contractility, and wall stress. Ischaemia-induced sympathetic activation can further increase the severity of ischaemia through a variety of mechanisms including a further increase of myocardial oxygen consumption and coronary vasoconstriction. The ischaemic cascade is characterized by a sequence of events, resulting in metabolic abnormalities, perfusion mismatch, regional and then global diastolic and systolic dysfunction, electrocardiographic (ECG) changes, and angina. Adenosine released by ischaemic myocardium appears to be the main mediator of angina (chest pain) through stimulation of A1 receptors located on cardiac nerve endings.<sup>4</sup> Ischaemia is followed by reversible contractile dysfunction known as 'stunning'. Recurrent episodes of ischaemia and

**Table 1** Recently published Guidelines and Consensus Statements that overlap with this guideline

Guideline	Developed by	Year of publication
European Guidelines on PCI in clinical practice	ESC	2005 <sup>587</sup>
ACC/AHA Guideline Update for Coronary Artery Bypass Graft Surgery	ACC/AHA	2004 <sup>614</sup>
Expert Consensus Document on angiotensin enzyme inhibitors in CVD	ESC	2004 <sup>676</sup>
Expert Consensus Document on $\beta$ -adrenergic receptor blockers	ESC	2004 <sup>677</sup>
Imaging techniques to detect myocardial hibernation. A report by the ESC Working Group	ESC	2004 <sup>199</sup>
Expert Consensus Document on the use of antiplatelet agents	ESC	2004 <sup>384</sup>
Evidence-based Guidelines for Cardiovascular Disease Prevention in Women	AHA, ACC, ACNP, ACOG, ACP, AMWA, ABC, CDCP, NHLBI, ORWH, STS, and WHF	2004 <sup>349</sup>
European guidelines on CVD prevention in clinical practice (Third Joint Task Force report)	ESC and other societies	2003 <sup>1</sup>
ACC/AHA/ASE Guideline Update for the Clinical Application of Echocardiography	ACC/AHA/ASE	2003 <sup>155</sup>
Consensus Statement American Society of Nuclear Cardiology: Task Force Report on Women and CAD. The role of myocardial perfusion imaging in the clinical evaluation of CAD in women	Am. Coll. of Nuclear Cardiology	2003 <sup>678</sup>
ACC/AHA Guideline Update for Exercise Testing	ACC/AHA	2002 <sup>140</sup>
ACC/AHA Guideline Update for the Management of Patients with Chronic Stable Angina	ACC/AHA	2002 <sup>379</sup>
ACC Clinical Expert Consensus Document on Standards for Acquisition, Measurement and Reporting of Intravascular Ultrasound Studies (IVUS)	ACC/ESC	2001 <sup>246</sup>
American College of Cardiology/American Heart Association Expert Consensus Document on Electron Beam Computed Tomography for the Diagnosis and Prognosis of CAD	ACC/AHA	2000 <sup>234</sup>
ACC/AHA Guidelines for Coronary Arteriography	ACC/AHA	1999 <sup>679</sup>
Management of stable angina pectoris. Recommendations of the Task Force of the European Society of Cardiology	ESC	1997 <sup>680</sup>
ESC Working Group on Exercise Physiology, Physiopathology, and Electrocardiography. Guidelines for Cardiac Exercise Testing	ESC	1993 <sup>135</sup>

stunning may lead to a chronic but still reversible form of dysfunction known as 'hibernation'. A brief episode of ischaemia results in 'preconditioning', a powerful endogenous form of protection which makes the heart more resistant to subsequent ischaemic episodes.<sup>5</sup>

Myocardial ischaemia may also be silent.<sup>6</sup> Lack of pain may be due to ischaemia of insufficient duration and/or severity, to damage of afferent cardiac nerves, or to inhibition of ischaemic cardiac pain at spinal or supraspinal level. In patients who exhibit painless ischaemia, shortness of breath, and palpitation may represent anginal equivalents. Breathlessness may be due to ischaemic left ventricular (LV) systolic or diastolic dysfunction or to transient ischaemic mitral regurgitation.

In the majority of patients, the pathological substrate of stable angina is atheromatous, narrowing of the coronary arteries. The normal vascular bed has the capacity to reduce resistance such that coronary blood flow increases by up to 5–6-fold during maximal exercise. Reduction in the luminal cross-sectional area by atherosclerotic plaque reduces the normal ability of the coronary vascular bed to reduce its resistance during maximal exercise with resultant ischaemia dependent on the degree of obstruction and myocardial oxygen demands. When luminal obstruction is  $\leq 40\%$  maximal flow during exercise can usually be maintained. But luminal diameter reduction of  $>50\%$  may be associated with ischaemia when coronary

blood flow becomes inadequate to meet cardiac metabolic demand during exercise or stress.<sup>7,8</sup> Stenosis resistance changes relatively little with mild degrees of vascular narrowing but rises precipitously with severe obstruction, with resistance almost tripling between stenosis of 80% and 90%. For a similar degree of stenosis, the ischaemic threshold is influenced by other factors including the degree of development of collateral circulation, the degree of transmural distribution of myocardial perfusion from the more vulnerable subendocardium to the subepicardium, coronary vascular tone, and platelet aggregation. Endothelial dysfunction as a cause of angina is discussed in Syndrome X. Rarely, angina may be caused by myocardial bridging.<sup>9</sup>

In stable angina, the angina threshold may vary considerably from day to day and even during the same day. Symptom variability is due to a variable degree of vasoconstriction at the site of critical stenoses (dynamic stenoses) and/or distal coronary vessels, depending on factors such as ambient temperature, mental stress, and neuro-hormonal influences.<sup>10</sup> In a sizeable proportion of patients, angina may occasionally occur even at rest.

Patients with stable angina are at risk of developing an ACS: unstable angina, non-ST-elevation MI or ST-elevation MI. Unstable angina is characterized by a sudden worsening of angina symptoms, which become more frequent, more prolonged, and more severe and/or occur at a lower threshold

or at rest.<sup>11</sup> MI is characterized by prolonged angina (>30 min) associated with myocardial necrosis.<sup>12</sup> Both non-ST-elevation and ST-elevation MI are frequently preceded by a period of days, or even weeks, of unstable symptoms. The common pathological background of ACS is erosion, fissure, or rupture of an atherosclerotic coronary plaque associated with platelet aggregation, leading to subtotal or total thrombotic coronary occlusion. Activated platelets release a number of vasoconstrictors, which may further impair coronary flow through the stimulation of vascular smooth muscle cells both locally and distally. The haemodynamic severity of the atherosclerotic plaque prior to destabilization is frequently mild and the plaques are lipid filled with foam cells. Intravascular ultrasound studies have shown that so-called vulnerable plaques (i.e. at risk of cap rupture) that are <50% in diameter both precede and predict future acute syndromes occurring precisely in their neighbourhood.<sup>13</sup> Activation of inflammatory cells within the atherosclerotic plaque appears to play an important role in the destabilization process,<sup>14</sup> leading to plaque erosion, fissure, or rupture. More recently, the concept of a single vulnerable plaque causing an ACS has been challenged in favour of a more generalized inflammatory response.<sup>15</sup>

## Epidemiology

As angina is essentially a diagnosis based on history, and therefore subjective, it is understandable that its prevalence and incidence have been difficult to assess and may vary between studies dependent on the definition that has been used.

For epidemiological purposes, the London School of Hygiene and Tropical Medicine cardiovascular questionnaire, devised by Rose and Blackburn<sup>16</sup> and adopted by the WHO, has been widely used. It defines angina as chest pain, pressure, or heaviness that limits exertion, is situated over the sternum or in the left chest and left arm, and is relieved within 10 min of rest. The questionnaire allows a subdivision of symptoms into definite and possible angina, which can be further subdivided into grade 1 and grade 2.<sup>17</sup> It should be recognized that this questionnaire is a screening tool and not a diagnostic test.

Rose angina questionnaire predicts cardiovascular morbidity and mortality in European<sup>18,19</sup> and American populations,<sup>20</sup> independent of other risk factors. Therefore, it has been indirectly validated. It has been compared with other standards including a clinical diagnosis,<sup>21</sup> ECG findings,<sup>22</sup> radionuclide tests,<sup>23</sup> and coronary arteriography.<sup>24</sup> On the basis of such comparisons, its specificity is ~80–95% but its sensitivity varies greatly from 20 to 80%. The exertional component of the symptoms is crucial to the diagnostic accuracy of the questionnaire,<sup>18</sup> and its performance seems to be less accurate in women.<sup>25</sup>

The prevalence of angina in community studies 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.<sup>26–33</sup> Therefore, it can be estimated that in most European countries, 20 000–40 000 individuals of the population per million suffer from angina.

Community-based information on the incidence of angina pectoris is derived from prospective, epidemiologic studies with repeated examinations of the cohort. Such studies

have been scarce over recent years. Available data, from the Seven Countries study,<sup>34</sup> studies in the UK,<sup>35,36</sup> the Israel Ischaemic Heart Disease study,<sup>37</sup> the Honolulu Heart study,<sup>38</sup> the Framingham study<sup>39,40</sup> and others,<sup>41</sup> suggest an annual incidence of uncomplicated angina pectoris of ~0.5% in western populations aged >40, but with geographic variations evident.

A more recent study, using a different definition of angina based on case description by clinicians, which defined angina pectoris as the association of chest pain at rest or on exertion with one positive finding from a cardiovascular examination such as arteriography, scintigraphy, exercise testing, or resting ECG,<sup>42</sup> confirm geographical variations in the incidence of angina which occur in parallel with observed international differences in coronary heart disease (CHD) mortality. The incidence of angina pectoris as a first coronary event was approximately twice high in Belfast compared with France (5.4 per 1000 person-years compared with 2.6).

Temporal trends suggest a decrease in the prevalence of angina pectoris in recent decades<sup>35,43</sup> in line with falling cardiovascular mortality rates observed in the MONICA<sup>44</sup> study. However, the prevalence of a history of diagnosed CHD does not appear to have decreased, suggesting that although fewer people are developing angina due to changes in lifestyle and risk factors, those who have coronary disease are living longer with the disease. Improved sensitivity of diagnostic tools may additionally contribute to the contemporary high prevalence of diagnosed CHD.

## 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 antianginal therapy, and observational registries, with selection bias an important factor to consider when evaluating and comparing the available data. European data estimate the cardiovascular disease (CVD) mortality rate and CHD mortality rates for men with Rose questionnaire angina to be between 2.6 and 17.6 per 1000 patient-years between the 1970s and 1990s.<sup>35,45</sup> Data from the Framingham Heart Study<sup>40,46</sup> showed that for men and women with an initial clinical presentation of stable angina, the 2-year incidence rates of non-fatal MI and CHD death were 14.3 and 5.5% in men and 6.2 and 3.8% in women, respectively. More contemporary data regarding prognosis can be gleaned from clinical trials of antianginal therapy and/or revascularization, although these data are biased by the selected nature of the populations studied. From these, estimates for annual mortality rates range from 0.9–1.4% per annum,<sup>47–51</sup> with an annual incidence of non-fatal MI between 0.5% (INVEST)<sup>50</sup> and 2.6% (TIBET).<sup>48</sup> These estimates are consistent with observational registry data.<sup>52</sup>

However, within the population with stable angina, an individual's prognosis can vary considerably, by up to 10-fold, dependent on baseline clinical, functional, and anatomical factors. Therefore, prognostic assessment is an important part of the management of patients with stable angina. On the one hand, it is important to carefully select those patients with more severe forms of disease and candidates for revascularization and potential

improvement in outcome with more aggressive investigation and treatment. On the other hand, it is also important to select those patients with a less severe form of disease, with a good outcome, thereby avoiding unnecessary invasive and non-invasive tests and procedures.

Conventional risk factors for the development of CAD,<sup>26,53–55,56</sup> hypertension, hypercholesterolaemia<sup>56–59</sup> diabetes,<sup>60–65</sup> and smoking<sup>26</sup> have an adverse influence on prognosis in those with established disease, presumably through their effect on disease progression. However, appropriate treatment can reduce or abolish these risks. Other factors predictive of long-term prognosis of patients with stable angina have been determined from the follow-up of the large control groups of randomized trials aimed at evaluating the effectiveness of revascularization<sup>66,67</sup> and other observational data. In general, the outcome is worse in patients with reduced LV function, a greater number of diseased vessels, more proximal locations of coronary stenosis, greater severity of lesions, more severe angina, more extensive ischaemia, and greater age.

LV function is the strongest predictor of survival in patients with chronic stable coronary disease; the next most important factor is the distribution and severity of coronary stenosis. Left main (LM) disease, three-vessel disease, and the proximal involvement of the left anterior descending are common characteristics predicting a poor outcome and increase the risk of ischaemic events.<sup>68</sup>

Myocardial revascularization can reduce the risk of death in selected anatomical subgroups,<sup>69</sup> reduce the number of ischaemic episodes (ACIP),<sup>70</sup> and in some instances may improve the LV function in high-risk patients.<sup>71,72</sup> However, disease progression and the occurrence of acute events may not necessarily be related to the severity of stenosis at coronary arteriography. In all patients, smaller lipid filled plaques are present in addition to those that cause severe stenoses. As discussed earlier, these 'vulnerable plaques' have a greater likelihood to rupture.<sup>14</sup> Thus, the risk of acute events is related to the overall plaque burden and to plaque vulnerability. Although an area of great research interest, our capabilities to identify vulnerable plaque remain limited.

## Diagnosis and assessment

Diagnosis and assessment of angina involves 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. Some should be used routinely in all patients; others provide redundant information except in particular circumstances; some should be easily available to cardiologists and general physicians, yet others may be considered as tools for research. In practice, diagnostic and prognostic assessments are conducted in tandem rather than separately, and many of the investigations used for 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 following section.

## 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 be 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, no more than 10 min in the majority of cases, and more commonly even minutes 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 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. Noncardiac causes of pain should be evaluated in such cases.

Definitions of typical and atypical angina have been previously published,<sup>73</sup> summarized on *Table 2*. It is

**Table 2** Clinical classification of chest pain

Typical angina (definite)	Meets three of the following characteristics <ul style="list-style-type: none"> <li>• Substernal chest discomfort of characteristic quality and duration</li> <li>• Provoked by exertion or emotional stress</li> <li>• Relieved by rest and/or GTN</li> </ul>
Atypical angina (probable)	Meets two of these characteristics
Non-cardiac chest pain	Meets one or none of the characteristics

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 the 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 and intensity and at lower threshold over a short period, 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 is dealt with in guidelines for the management of ACS.

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 3). This is useful in determining the functional impairment of the patient and quantifying response to therapy. The Canadian Cardiovascular Society Classification<sup>74</sup> is widely used as a grading system for angina to quantify the threshold at which symptoms occur in relation to physical activities. Alternative classification systems such as Duke Specific Activity Index<sup>75</sup> and Seattle angina questionnaire<sup>76</sup> may also be used in determining the functional impairment of the patient and quantifying response to therapy and may offer superior prognostic capability.<sup>77</sup>

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 assessment of body-mass index (BMI) and waist circumference to assist evaluation of the metabolic syndrome,<sup>78,79</sup> evidence of non-coronary vascular disease which may be asymptomatic, and other signs of comorbid conditions. However, there are no specific signs in angina pectoris. During or immediately after an episode of myocardial ischaemia, a third or fourth heart sound may be heard and mitral insufficiency may also be apparent during ischaemia. Such signs are, however, elusive and non-specific.

**Table 3** 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 <sup>a</sup> on the level or one flight of stairs at a normal pace under normal conditions
Class IV	'Inability to carry out any physical activity without discomfort' or 'angina at rest'

<sup>a</sup>Equivalent to 100–200 m.

### 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. Some laboratory investigations are used for more than one of these purposes and may be applied routinely in all patients, whereas other investigations should be reserved for use where clinical history and/or examination indicates a particular need for their application.

Haemoglobin and, where there is 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.<sup>80</sup> If there is clinical suspicion of instability, biochemical markers of myocardial damage such as troponin or CKMB (creatinine kinase myocardial band), measured by mass assay, should be employed to exclude myocardial injury. If these markers are elevated, management should continue as for an ACS rather than stable angina. After initial assessment, these tests are not recommended as routine investigations during each subsequent evaluation.

Fasting plasma glucose<sup>60,61,63,64,81,82,83,84</sup> and fasting lipid profile including total cholesterol (TC), high density lipoprotein (HDL) cholesterol, and low density lipoprotein (LDL) cholesterol,<sup>55–58</sup> and triglycerides<sup>54,85</sup> 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 reassessment should take place. Consensus suggests annual measurement. Patients with very high levels of lipids, in whom the progress of any intervention needs to be monitored, should have measurements more frequently. Patients with diabetes should be managed accordingly.

Serum creatinine is a simple but crude method to evaluate renal function. Renal dysfunction may occur due to associated comorbidity<sup>86–91</sup> such as hypertension, diabetes or renovascular disease and has a negative impact on prognosis in patients with CVD,<sup>92,93</sup> giving good grounds for measurement at initial evaluation in all patients with suspected angina. The Cockcroft–Gault formula<sup>94</sup> may be used to estimate creatinine clearance based on age, sex, weight, and serum creatinine. The commonly used formula is as follows:  $((140 - \text{age (years)}) \times (\text{actual weight (kg)})) / (72 \times \text{serum creatinine (mg/dL)})$ , with multiplication by a factor of 0.85 if female.

In addition to the well-recognized association between adverse cardiovascular outcome and diabetes, elevations of fasting or post-glucose challenge glycaemia have also been shown to predict adverse outcome in stable coronary disease independently of conventional risk factors.<sup>95–101</sup> Although HbA1c predicts outcome in the general population, there is less data in those with CAD.<sup>101,102</sup> Obesity, and in particular evidence of the metabolic syndrome, is predictive of adverse cardiovascular outcome in patients with established disease as well as asymptomatic populations.<sup>78,79,103</sup> The presence of the metabolic syndrome can be determined

from assessment of waist circumference (or BMI), blood pressure, HDL, triglycerides, and fasting glucose levels and offers additional prognostic information to that obtained from conventional Framingham risk scores<sup>104</sup> without major additional cost in terms of laboratory investigation.

Further laboratory testing, including cholesterol subfractions (ApoA and ApoB)<sup>105,106</sup> homocysteine,<sup>107,108</sup> lipoprotein (a) (Lpa), haemostatic abnormalities,<sup>109–112</sup> and markers of inflammation such as hs-C-reactive protein,<sup>56,113,114</sup> have been the subject of much interest as methods to improve current risk prediction.<sup>113,115</sup> However, markers of inflammation fluctuate over time and may not be a reliable estimator of risk in the longer term.<sup>116</sup> 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.<sup>117</sup> As yet, there is inadequate 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,<sup>118</sup> or a strong family history of coronary disease, or where resources are not limited. Further research into their use is welcomed. The use of glycated haemoglobin or response to oral glucose load in addition to a single measurement of fasting plasma glucose have also been shown to improve detection of glycaemic abnormalities, but as yet there is insufficient evidence to recommend this strategy in all patients with chest pain.<sup>119,120</sup> This may be a useful method of detecting glycaemic abnormalities in selected patients particularly at high risk for their development.

#### **Recommendations for laboratory investigation in initial assessment of stable 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 white cell count (level of evidence B)
- (4) Creatinine (level of evidence C)

Class I (if specifically indicated on the basis of clinical evaluation)

- (1) Markers of myocardial damage if evaluation suggests clinical instability or ACS (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 reassessment 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 risk stratification. The test should be requested only in patients with suspected heart failure,<sup>121,122</sup> valvular disease, or pulmonary disease. The presence of cardiomegaly, pulmonary congestion, atrial enlargement, and cardiac calcifications has been related to impaired prognosis.<sup>123–128</sup>

#### **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, and recommendations for risk stratification will be dealt with in the following section. As there are few randomized trials assessing health outcomes for diagnostic tests, the available evidence has been ranked according to 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 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 MI 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,<sup>129,130</sup> 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), left bundle branch block (LBBB), 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 Risk Stratification section.<sup>131–133</sup>

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 reassessment 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<sup>134,135</sup> 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.<sup>136-139</sup> Using exercise ST-depression  $<0.1$  mV or 1 mm to define a positive test, the reported sensitivity and specificity for the detection of significant coronary disease range between 23–100% (mean 68%) and 17–100% (mean 77%), respectively. Excluding patients with prior MI, the mean sensitivity was 67% and specificity 72%, and restricting analysis to those studies designed to avoid work-up bias, sensitivity was 50% and specificity 90%.<sup>140</sup> The majority of reports are of studies where the population tested did not have significant ECG abnormalities at baseline and were not on antianginal therapy or were withdrawn from antianginal therapy for the purposes of the test. Exercise ECG testing is not of diagnostic value in the presence of 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.<sup>141</sup>

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.<sup>142</sup> 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, as outlined in *Table 4*.

In populations with a low prevalence of ischaemic heart disease the proportion of false-positive tests will be high when compared with a population with a high pre test probability of disease. Conversely, in male patients with severe effort angina, with clear ECG changes during pain, the pretest probability of significant coronary disease is high ( $>90\%$ ), and in such cases, the exercise test will not offer additional information for the diagnosis, although it may add prognostic information.

A further factor that may influence the performance of the exercise ECG as a diagnostic tool is the definition of a positive test. ECG changes associated with myocardial ischaemia include horizontal or down-sloping ST-segment depression or elevation [ $\geq 1$  mm (0.1 mV) for  $\geq 60$ –80 ms after the end of the QRS complex], especially when these changes are accompanied by chest pain suggestive of angina, occur at a low workload during the early stages of exercise and persist for more than 3 min after exercise. Increasing the threshold for a positive test, for example, to  $\geq 2$  mm (0.2 mV) ST-depression, will increase specificity at the expense of sensitivity. A fall in systolic pressure or lack of increase of blood pressure during exercise and the appearance of a systolic murmur of mitral regurgitation or ventricular arrhythmias during exercise reflect impaired LV function and increase the probability of severe myocardial ischaemia and severe CAD. 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.<sup>143</sup> It has been suggested that evaluating ST changes in relation to heart rate improves reliability of diagnosis<sup>144</sup> but this may not be so in symptomatic populations.<sup>145-147</sup>

An exercise test should be carried out only after careful clinical evaluation of symptoms and a physical examination including resting ECG.<sup>135,140</sup> Complications during exercise testing are few but severe arrhythmias and even sudden death can occur. Death and MI occur at a rate of less than or equal to one per 2500 tests.<sup>148</sup> Accordingly, exercise testing should only be performed under careful monitoring in the appropriate setting. A physician should be present or immediately available to monitor the test. The ECG should be continuously recorded with a printout at pre-selected intervals, mostly at each minute during exercise, and 2–10 min of recovery after exercise. 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.

Either the Bruce protocol or one of its modifications on a treadmill or a bicycle ergometer can be employed. Most consist of several stages of exercise, increasing in intensity, either speed, slope, or resistance or a combination of these factors, at fixed intervals, to test functional capacity. It is convenient to express oxygen uptake in multiples of resting requirements. One metabolic equivalent (MET) is a unit of sitting/resting oxygen uptake [3.5 mL of O<sub>2</sub> per kilogram of body weight per minute (mL/kg/min)].<sup>149</sup> Bicycle workload is frequently described in terms of watts (W). Increments are of 20 W per 1 min stage starting from 20 to 50 W, but increments may be reduced to 10 W per stage in patients with heart failure or severe angina. Correlation between METs achieved and workload in watts varies with numerous patient-specific and environmental factors.<sup>135,150</sup>

The reason for stopping the test and the symptoms at that time, including their severity, should be recorded. Time to the 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, and the post-exercise recovery rate of ECG changes and heart rate should also be assessed. For repeated exercise tests, the

**Table 4** Probability of coronary disease in symptomatic patients based on (a) age, gender, and symptom classification and (b) modified by exercise test results

(a) Pretest likelihood of CAD in symptomatic patients according to age and sex

Age (years)	Typical angina		Atypical angina		Non-anginal chest pain	
	Male	Female	Male	Female	Male	Female
30–39	69.7 ± 3.2	25.8 ± 6.6	21.8 ± 2.4	4.2 ± 1.3	5.2 ± 0.8	0.8 ± 0.3
40–49	87.3 ± 1.0	55.2 ± 6.5	46.1 ± 1.8	13.3 ± 2.9	14.1 ± 1.3	2.8 ± 0.7
50–59	92.0 ± 0.6	79.4 ± 2.4	58.9 ± 1.5	32.4 ± 3.0	21.5 ± 1.7	8.4 ± 1.2
60–69	94.3 ± 0.4	90.1 ± 1.0	67.1 ± 1.3	54.4 ± 2.4	28.1 ± 1.9	18.6 ± 1.9

(b) CAD post-test likelihood (%) based on age, sex, symptom classification and exercise-induced electrocardiographic ST-segment depression

Age (years)	ST-depression (mV)	Typical angina		Atypical angina		Non-anginal chest pain		Asymptomatic	
		Male	Female	Male	Female	Male	Female	Male	Female
30–39	0.00–0.04	25	7	6	1	1	<1	<1	<1
	0.05–0.09	68	24	21	4	5	1	2	4
	0.00–0.14	83	42	38	9	10	2	4	<1
	0.00–0.19	91	59	55	15	19	3	7	1
	0.00–0.24	96	79	76	33	39	8	18	3
40–49	>0.25	99	93	92	63	68	24	43	11
	0.00–0.04	61	22	16	3	4	1	1	<1
	0.00–0.09	86	53	44	12	13	3	5	1
	0.00–0.14	94	72	64	25	26	6	11	2
	0.00–0.19	97	84	78	39	41	11	20	4
50–59	0.00–0.24	99	93	91	63	65	24	39	10
	>0.25	>99	98	97	86	87	53	69	28
	0.00–0.04	73	47	25	10	6	2	2	1
	0.00–0.09	91	78	57	31	20	8	9	3
	0.00–0.14	96	89	75	50	37	16	19	7
60–69	0.00–0.19	98	94	86	67	53	28	31	12
	0.00–0.24	99	98	94	84	75	50	54	27
	>0.25	>99	99	98	95	91	78	81	56
	0.00–0.04	79	69	32	21	8	5	3	2
	0.00–0.09	94	90	65	52	26	17	11	7
	0.00–0.14	97	95	81	72	45	33	23	15
	0.00–0.19	99	98	89	83	62	49	37	25
	0.00–0.24	99	99	96	93	81	72	61	47
	>0.25	>99	99	99	98	94	90	85	76

use of the Borg scale or similar method of quantifying symptoms may be used to allow comparisons.<sup>151</sup> Reasons to terminate an exercise test are listed in *Table 5*.

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 if 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.<sup>135</sup> 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 for prognostic stratification,<sup>152</sup> 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.

#### Recommendations for exercise ECG for initial diagnostic assessment of angina

##### Class I

- (1) Patients with symptoms of angina and intermediate 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) In patients with low pre-test probability (<10% probability) of coronary disease based on age, gender, and symptoms (level of evidence B)

**Table 5** Reasons to terminate the exercise stress test

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

- Symptom limitation, e.g. pain, fatigue, dyspnoea, and claudication
- Combination of symptoms such as pain with significant ST-changes
- Safety reasons such as the following
  - 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)
  - ST-elevation ≥1 mm
  - Significant arrhythmia
  - Sustained fall in systolic blood pressure >10 mmHg
  - Marked hypertension (>250 mmHg systolic or >115 mmHg diastolic)
- 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 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 assessment over the past two decades or more. Novel stress imaging techniques also include stress MRI, which, for logistical reasons, is most frequently performed using pharmacological rather than exercise stress.

Stress imaging techniques have several advantages over conventional exercise ECG testing including superior diagnostic performance (*Table 6*) for the detection of obstructive coronary disease, the ability to quantify and localize areas of ischaemia, and 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 PCI or coronary artery bypass grafting (CABG) because of its 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 reassured.<sup>153</sup>

**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

**Table 6** 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

during each stage of exercise and at peak exercise. This may be technically challenging.<sup>154</sup> Reported sensitivities and specificities for the detection of significant coronary disease are within a similar range to those described for exercise stress perfusion scintigraphy, sensitivity 53–93% specificity 70–100%, although stress echo tends to be less sensitive and more specific than stress perfusion scintigraphy. Depending on the meta-analysis, overall sensitivity and specificity of exercise echocardiography are reported as 80–85 and 84–86%.<sup>155–158</sup> 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.<sup>159–161</sup> 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 velocity between adjacent regions and strain rate being the difference per unit length. Tissue Doppler imaging<sup>162,163</sup> and strain rate imaging<sup>164,165</sup> have improved the diagnostic performance of stress echocardiography<sup>166</sup> improving the capability of echocardiography to detect ischaemia earlier in the ischaemic cascade.<sup>166,167</sup> 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.<sup>168</sup>

**Exercise testing with myocardial perfusion scintigraphy.** <sup>201</sup>Th and <sup>99m</sup>Tc 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. Regardless of the radiopharmaceutical used, SPECT perfusion scintigraphy is performed to produce

images of regional tracer uptake that reflect relative regional myocardial blood flow. With this technique, myocardial hypoperfusion is characterized by reduced tracer uptake during stress in comparison with the uptake at rest. Increased uptake of myocardial perfusion agent in the lung field identifies patients with severe and extensive coronary artery disease (CAD)<sup>169–172</sup> and stress-induced ventricular dysfunction.<sup>173</sup> SPECT perfusion provides a more sensitive and specific prediction of the presence of CAD than exercise ECG. Without correction for referral bias, the reported sensitivity of exercise scintigraphy has generally ranged from 70–98%, and specificity from 40–90%, with mean values in the range of 85–90% and 70–75% depending on the meta-analysis.<sup>157,158,171,174</sup>

**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: Either (i) infusion of short-acting sympatho-mimetic 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, with major cardiac complications (including sustained VT) occurring every 1500 tests with dipyridamole, or one in every 300 with dobutamine.<sup>156,175–177</sup> 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. Dobutamine does not provoke as great an increase in coronary blood flow as vasodilator stress, which is a limitation for perfusion scintigraphy. Thus, for this technique dobutamine is mostly reserved for patients who cannot exercise and have a contraindication to vasodilator stress.<sup>178</sup> The diagnostic performance of pharmacological stress perfusion and pharmacological stress echo are also similar to that of exercise imaging techniques. Reported sensitivity and specificity for dobutamine stress echo range from 40–100% and 62–100%, respectively, and 56–92% and 87–100% for vasodilator stress.<sup>156,157</sup> Sensitivity and specificity for the detection of coronary disease with adenosine SPECT range from 83–94% and 64–90%.<sup>157</sup>

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 the greater availability and lower cost, in addition to being free of radiation. However, at least 5–10% of patients have an inadequate echo window, and special training in addition to standard echocardiographic training is required to correctly perform and interpret stress echocardiograms. Nuclear scintigraphy also requires special training for performance and interpretation of the tests. The development of quantitative echocardiographic techniques such as tissue Doppler imaging is a step towards increasing the inter-observer agreement and reliability of stress echo.

Non-invasive diagnosis of CAD in patients with LBBB or with permanent pacemaker *in situ* remains challenging for both stress echocardiography and stress scintigraphic techniques,<sup>179,180</sup> although stress perfusion imaging is markedly less specific in this setting.<sup>181–184</sup> Very poor accuracy is reported for both stress perfusion and stress echocardiography in patients with ventricular dysfunction associated with LBBB.<sup>185</sup> Stress echo has also been shown to have prognostic value even in the setting of LBBB.<sup>186</sup>

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. These are not limited to the immediate financial costs of the individual test, where some of the cost effectiveness analyses have been favourable in certain settings.<sup>187,188</sup> But other factors such as limited availability of testing facilities and expertise, with consequently increased waiting times for testing the majority of patients attending the evaluation of angina must also be considered. The resource redistribution and training implications of ensuring adequate access for all patients are considerable, and the benefits to be obtained by a change from exercise ECG to stress imaging in all patients are not sufficiently great to warrant recommendation of stress imaging as a universal first line investigation. However, stress imaging has an important role to play in evaluating patients with a low pre-test probability of disease, particularly women,<sup>189–192</sup> when exercise testing is inconclusive, in selecting lesions for revascularization, and in assessing ischaemia after revascularization.<sup>193–196</sup> Pharmacologic stress imaging may also be used in the identification of viable myocardium in selected patients with coronary disease and ventricular dysfunction in whom a decision for revascularization will be based on the presence of viable myocardium.<sup>197,198</sup> A full description of the methods of detection of 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.<sup>199</sup> 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, cost, 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 above if the patient is unable to exercise adequately.

**Stress cardiac magnetic resonance.** CMR stress testing in conjunction with a dobutamine infusion can be used to detect wall motion abnormalities induced by ischaemia. The technique has been shown to compare favourably to dobutamine stress echocardiography (DSE) because of higher quality imaging.<sup>200</sup> Thus, dobutamine stress CMR has been shown to be very effective in the diagnosis of CAD in patients who are unsuitable for dobutamine echocardiography.<sup>201</sup> Studies of outcome following dobutamine CMR show a low event rate when dobutamine CMR is normal.<sup>202</sup>

Myocardial perfusion CMR now achieves comprehensive ventricular coverage using multislice imaging. Analysis is either visual to identify low signal areas of reduced perfusion, or with computer assistance with quantification of the upslope of myocardial signal increase during the first pass. Although CMR perfusion is still in development for clinical application, the results are already very good in comparison with X-ray coronary angiography, PET, and SPECT.<sup>203,204</sup>

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).<sup>205</sup>

#### **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<sup>206</sup> or hypertrophic cardiomyopathy<sup>207</sup> as a cause of symptoms, and to evaluate ventricular function.<sup>155</sup> For purely diagnostic purposes, echo is useful in patients with clinically detected murmurs,<sup>208–211</sup> history and ECG changes compatible with hypertrophic

cardiomyopathy<sup>207,212</sup> or previous MI,<sup>213,214</sup> and symptoms or signs of heart failure.<sup>215–219</sup> Cardiac magnetic resonance may be also be used to define structural cardiac abnormalities and evaluate ventricular function, but routine use for such purposes is limited by availability.

The true prevalence of isolated diastolic heart failure is difficult to quantify because of heterogeneity in definitions and variability in populations studied.<sup>220</sup> Community-based studies have an independent association between diastolic heart failure and a history of ischaemic heart disease, including angina,<sup>221</sup> strengthening the case for echocardiography in all patients with angina, and signs or symptoms of heart failure. Universal resting echocardiography in a stable angina population without heart failure may also identify previously undetected diastolic dysfunction. Recent developments in tissue Doppler imaging and strain rate measurement have greatly improved the ability to study diastolic function<sup>165,222</sup> but the clinical implications of isolated diastolic dysfunction in terms of treatment or prognosis are less well defined. Diastolic function may improve with anti-ischaemic therapy.<sup>223</sup> However, treatment of diastolic dysfunction as a primary aim of therapy in stable angina is not yet warranted. There is no indication for repeated use of resting echocardiography on a regular basis in patients with uncomplicated stable angina in the absence of a change in clinical condition.

Although the diagnostic yield of evaluation of cardiac structure and function in patients with angina is mostly concentrated in specific subgroups, 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 ECG LVH (level of evidence C)

#### **Ambulatory ECG monitoring**

Ambulatory ECG (Holter) monitoring may reveal evidence of myocardial ischaemia during normal 'daily' activities,<sup>224</sup> but rarely adds important diagnostic information in chronic stable angina pectoris over and above that provided by an exercise test.<sup>6</sup> Ambulatory silent ischaemia<sup>6</sup> has been reported to predict adverse coronary events and there is conflicting evidence that the suppression of silent ischaemia in stable angina improves cardiac outcome. The significance of silent ischaemia in this context is different from that in unstable angina where it has been shown that recurrent silent ischaemia predicts an adverse outcome. Prognostic studies in stable angina seem to identify silent ischaemia on ambulatory monitoring as a harbinger of hard clinical events (fatal and non-fatal MI) only in highly selected patients with ischaemia detectable on exercise testing,

and there is little evidence to support its routine deployment as a prognostic implement in this clinical setting.<sup>225,226</sup>

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.** Although spatial resolution and movement artefact have for a long time been limiting factors in computed tomography (CT) cardiac imaging, considerable advances in technology have been made in recent years to overcome these issues. Two modalities of CT imaging have developed to improve spatial and temporal resolution in CT, ultra-fast or electron beam CT (EBCT), and multi-detector or multi-slice CT (MDCT). These have been accompanied by improvements in processing software to facilitate interpretation of the images acquired. Both techniques have been validated as effective in the detection of coronary calcium and quantification of the extent of coronary calcification.<sup>227–230</sup> The Agatston score,<sup>231</sup> 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.

Calcium is deposited in atherosclerotic plaques within the coronary arteries. Coronary calcification increases with age, and nomograms have been developed to facilitate interpretation of calcium scores relative to the expected values for a given age and gender.<sup>232</sup> The extent of coronary calcification correlates more closely with the overall burden of plaque than with the location or severity of stenoses.<sup>233</sup> Thus 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.<sup>234,235</sup>

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.<sup>236</sup> MDCT or multi-slice CT appears to be 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 has been reported to be 95 and 98%, respectively, using 16-slice CT scanners.<sup>237</sup> 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%.<sup>238,239</sup> Non-invasive CT arteriography holds considerable promise for the future of

the diagnostic assessment of coronary disease. Optimal use of this rapidly developing technology will harness the skills of both radiology and cardiology disciplines, with cardiology necessarily taking the lead in selection of patients for investigation by this method, and appropriate management based on the results. At present, although the diagnostic accuracy of this technique has been reported, the prognostic utility, and the exact place in the hierarchy of investigations in stable angina has not yet been fully defined. A conservative suggestion for its use 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.** Similar to the case of CT, advances in magnetic resonance technology permit non-invasive MR contrast coronary arteriography,<sup>205</sup> and hold the potential for plaque characterization.<sup>240</sup> Advantages of the technique include the considerable potential for evaluation of overall cardiac anatomy and function. 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.<sup>241,242</sup> In addition, 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. Methods used to perform coronary arteriography have improved substantially resulting in the reduction of complication rates and rapid ambulation. The composite rate of major complications associated with routine diagnostic catheterization in patients is between 1 and 2%. The composite rate of death, MI, or stroke is of the order of 0.1–0.2%.<sup>243</sup>

##### **Intravascular ultrasound**

Intravascular ultrasound is a technique that allows production of ultrasound images from within the (coronary)

arteries by passing an ultrasound catheter into the coronary artery lumen.<sup>244</sup> Intravascular ultrasound allows for accurate measurement of coronary luminal diameter, assessment of eccentric lesions and Glagovian remodelling, and quantification of atheroma and calcium deposition. It also allows for detailed assessment of interventional target lesions, stent placement, apposition and expansion, and transplant vasculopathy. The technique has afforded advantages in terms of our understanding of atherosclerotic plaque deposition and progression, offering considerably improved qualitative and quantitative assessment of coronary anatomy compared with contrast arteriography and doubtless, has an important role in specialized clinical settings, particularly as an adjunct to coronary intervention. However, it is more appropriately used in highly specific clinical settings and for research purposes than widespread application as a first line investigation for coronary disease.<sup>245,246</sup>

### Invasive assessment of functional severity of coronary lesions

The functional severity of coronary lesions visualized angiographically may be assessed invasively by means of measuring either the coronary flow velocity (coronary vasodilatory reserve), or intracoronary artery pressure fractional flow reserve (FFR).<sup>7,247</sup> Both techniques involve inducing hyperaemia through intracoronary injection of vasodilating agents. The coronary vasodilatory reserve (CVR) is the ratio of hyperaemic to basal flow velocity and reflects flow resistance through the epicardial artery and the corresponding myocardial bed. It is dependent on microcirculation as well as severity of the lesion in the epicardial vessel. FFR<sup>248</sup> is calculated as the ratio of distal coronary pressure to aortic pressure measured during maximal hyperaemia. A normal value for FFR is 1.0 regardless of the status of the microcirculation, and an FFR <0.75 is deemed pathological.

Physiological measurements as described may facilitate diagnosis in cases of intermediate angiographic stenoses, (visually estimated stenosis 30–70%). FFR measurement has been shown to be useful in differentiating between patients with favourable long-term outcome (i.e. patients with FFR >0.75) who do not need revascularization; and patients who require revascularization (i.e. patients with FFR <0.75)<sup>249</sup> but this investigation is best reserved for specific clinical circumstances or in deciding suitability for revascularization rather than routine use.

### 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 MI, 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 purpose of implementing primary prevention guidelines.<sup>250</sup> However, absolute levels of what constitutes high-risk and low-risk are not clearly defined for those with established CVD.<sup>68,251</sup> This problem is linked to difficulties in comparing risk prediction systems across different populations, determining 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 (since 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 an estimation of what may be accepted as constituting high, low, and intermediate risk in a contemporary setting for the purposes of determining the threshold for invasive investigation or intensified pharmacological therapy.

The cardiovascular mortality and MI rate observed in the placebo arms of large trials of secondary prevention or

anti-anginal therapy in stable coronary disease published since 2000 are illustrated in *Figure 1*. The rate of cardiovascular death in the PEACE<sup>252</sup> study was less than 1% per annum, whereas in 'high-risk' populations such as in diabetic MICRO-HOPE<sup>253</sup> population and the IONA<sup>254</sup> 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.<sup>66–68,124,255,256</sup> However, not all patients will require invasive assessment of the coronary anatomy, particularly if their clinical evaluation and non-invasive testing establish that they are in a low-risk group. The risk assessment hierarchy can be described as:

- (1) Risk stratification by clinical evaluation
- (2) Risk stratification by response to stress testing
- (3) Risk stratification by ventricular function
- (4) Risk stratification by coronary anatomy

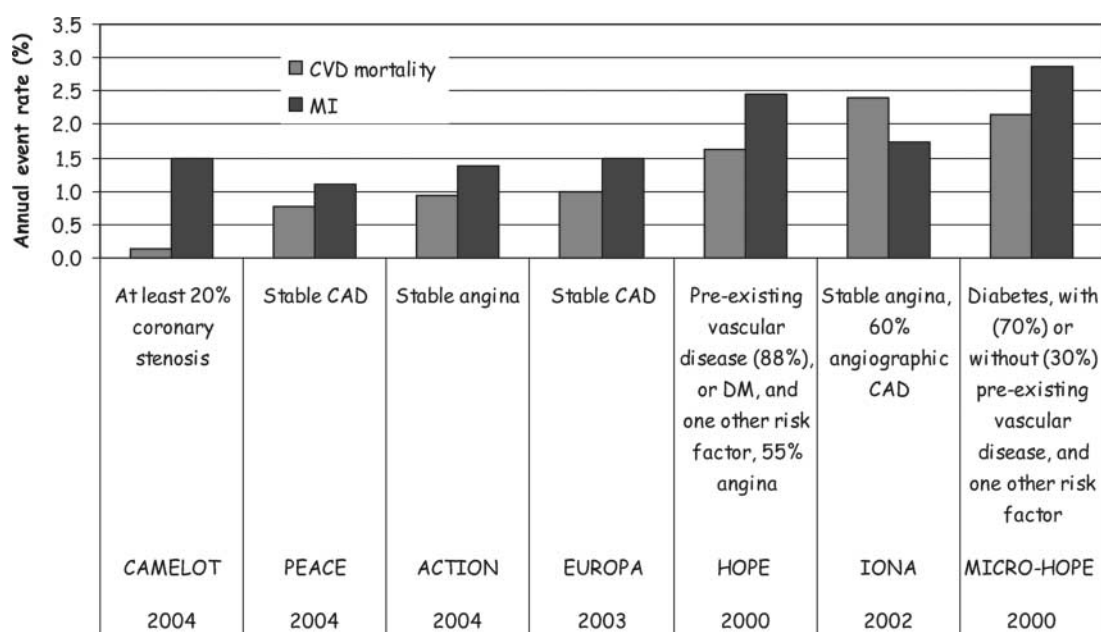
The route through these successive tests may not always be directly linear. For example in a patient with a high pre-test probability of disease, severe angina, and other high-risk clinical features such as signs of heart failure, may proceed directly from clinical evaluation to coronary arteriography, with perfusion scintigraphy afterwards to evaluate myocardial viability. However, 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. A summary of the recommendations for the routine use of investigations in evaluation of stable angina with corresponding levels of evidence related to diagnosis and prognosis, is presented in *Table 7*, and an algorithm for the initial evaluation of patients presenting with clinical symptoms suggestive of angina is depicted in *Figure 2*.

### Risk stratification using clinical evaluation

The clinical history and physical examination can provide very important prognostic information. ECG 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, 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.<sup>56,58,257–259</sup> Increasing age is an important factor to consider, as are prior MI,<sup>66,123</sup> symptoms and signs of heart failure,<sup>66,123,124</sup> and the pattern of occurrence (recent onset or progressive), and severity of angina, particularly if unresponsive to therapy.<sup>255,260</sup>

Pryor *et al.*<sup>261</sup> studied a total of 1030 consecutive outpatients referred to non-invasive testing for suspected CAD; the information from the initial history, physical examination, ECG, and chest radiograph was used to predict coronary anatomy, i.e. the likelihood of any significant coronary disease, severe disease, and significant left main (LM) disease and to estimate 3 years survival. These estimates were compared with those based on treadmill testing. Compared with the treadmill exercise test, initial evaluation was slightly better able to distinguish patients with or without CAD and was similar in the ability to identify patients at increased risk for dying or with anatomically severe disease. Although much of the information obtained by physicians during the initial assessment is



**Figure 1** Cardiovascular mortality and myocardial infarction in contemporary trials of stable coronary disease or angina: CAMELOT,<sup>467</sup> PEACE,<sup>252</sup> ACTION,<sup>493</sup> EUROPA,<sup>461</sup> HOPE,<sup>460</sup> IONA,<sup>254</sup> and MICRO-HOPE.<sup>253</sup>



**Table 7** 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
<b>Laboratory tests</b>				
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, and apoB	IIb	B	IIb	B
<b>ECG</b>				
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 vasospastic angina	IIa	C		
In suspected angina with normal exercise test	IIa	C		
<b>CXR</b>				
Suspected heart failure or abnormal cardiac auscultation	I	B	I	B
Suspected significant pulmonary disease	I	B		
<b>Echocardiogram</b>				
Suspected heart failure, abnormal auscultation, abnormal ECG, Qwaves, BBB, and 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
<b>Exercise ECG</b>				
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
<b>Exercise imaging technique (echo or radionuclide)</b>				
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		
<b>Pharmacological stress imaging technique</b>				
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	IIa	B	IIa	B
<b>Non-invasive CT arteriography</b>				
Patients with low probability of disease and non-conclusive or positive stress test	IIb	C		

subjective, their study confirms the importance of that information in identifying patients likely to benefit from further testing and supports the development of strategies that use the physician's initial assessment in the evaluation process.

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 3*) to predict outcome, particularly in the first year after assessment.

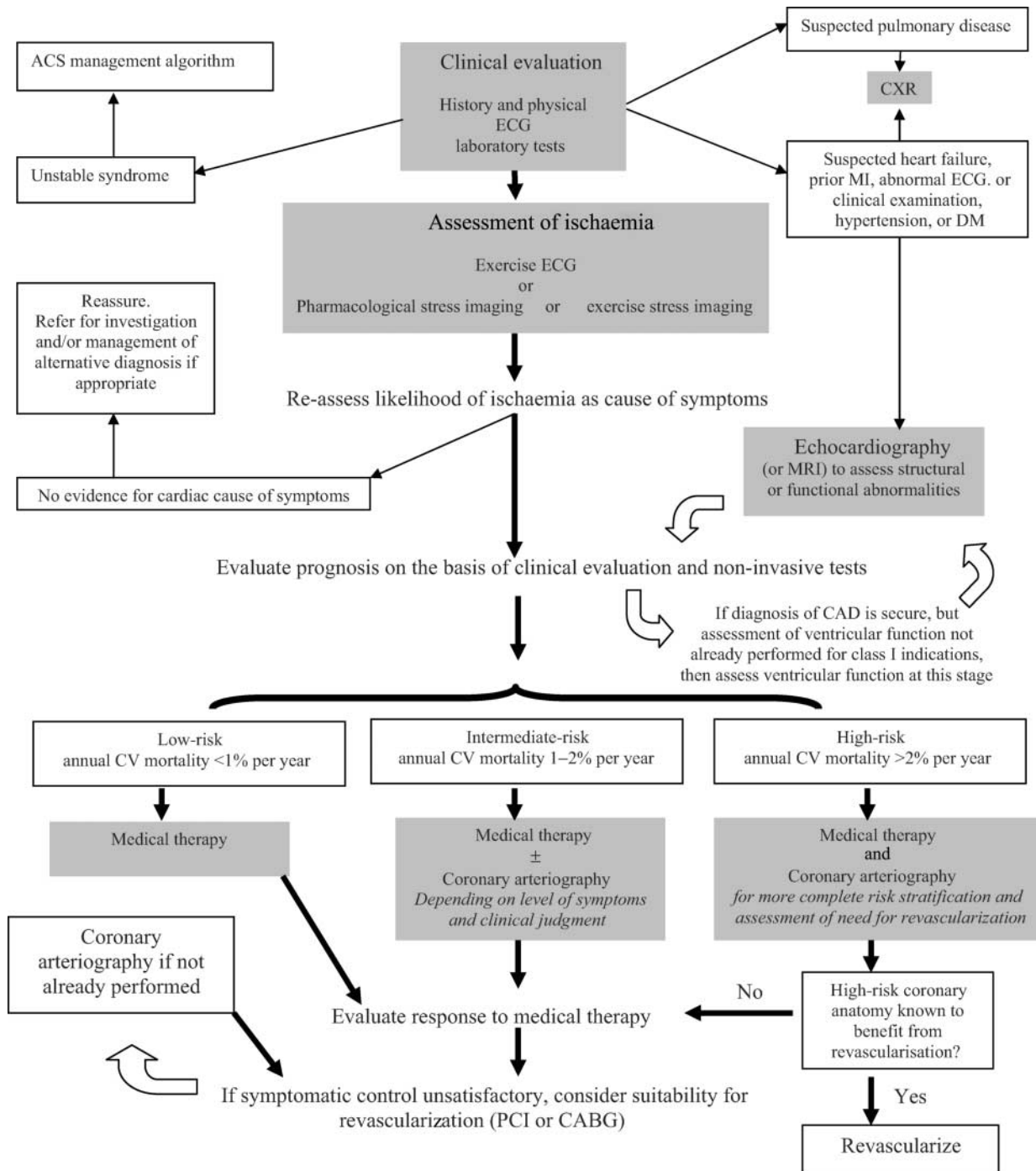


Figure 2 Algorithm for the initial evaluation of patients with clinical symptoms of angina.

The effect of angina score on prognosis is not apparent after 3 years and is greatest when ventricular function is maintained.<sup>68,255</sup> This is due to the profound effect of impaired ventricular function on prognosis, which when present, greatly outweighs the effect of symptom severity. The association between the pattern of angina occurrence, particularly the development of new onset symptoms, with adverse prognosis may be due to overlap with the milder end of the spectrum of unstable angina. Furthermore, with more severe angina, the likelihood of coronary revascularization for prognostically important

disease increases, which may also contribute to the time-dependency of symptom severity in predicting risk. Physical examination may also help in determining risk. The presence of peripheral vascular disease<sup>262,263</sup> (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. 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 AF are at greater

$\text{Score} = \text{angina course} \times (1 + \text{frequency}) + \text{ST/T abnormalities}$		
Stable = 0	(up to 5)	(6 points)
Progressive = 1		
Nocturnal pain = 2		
Unstable = 3		

Figure 3 Prognostic angina score. The pattern of angina occurrence can be used to predict prognosis.<sup>80</sup>

risk of future cardiovascular events than those with a normal ECG.<sup>45,264–267</sup> 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 just to 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. In addition to the limitations of the different techniques in the detection of myocardial ischaemia, however small, it must also be recognized that ischaemia *per se* is not the only factor which influences the likelihood of acute events. Several lines of evidence have shown that the majority of vulnerable plaques appear angiographically insignificant before their rupture, and may not impinge on coronary flow to reveal characteristic changes during exercise ECG or stress imaging. This may explain the occasional acute coronary event that occurs shortly after a negative stress test result. 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 prognosis of patients with a normal ECG and a low clinical risk for severe CAD is excellent. In one study in which 37% of outpatients referred for non-invasive testing met the criteria for low risk<sup>261</sup> fewer than 1% had LM stem artery disease or died within 3 years. Lower-cost options such as treadmill testing should therefore be used, whenever possible, for initial risk stratification, and only those with abnormal results should be referred to arteriography.

The prognostic exercise testing markers include exercise capacity, blood pressure response, and exercise-induced ischaemia (clinical and ECG). 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.<sup>139,268</sup> However, exercise capacity is also affected by age, general physical condition, comorbidities, 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.<sup>123,139,152,269,270</sup>

Other prognostic exercise testing markers are related to exercise-induced ischaemia and markers include changes in ST-segment (depression or elevation), and exercise-induced angina. McNeer *et al.*<sup>270</sup> demonstrated that an early positive exercise test (ST-depression >1 mm in the first two stages of the Bruce protocol) identified a high-risk population, whereas patients who could exercise into stage IV were at low risk regardless of the ST response. ST-segment elevation is observed most frequently in patients with a history of MI; in patients without infarction, ST-elevation during exercise has been associated with severe transmural myocardial ischaemia.

In the CASS Registry, 12% of medically treated patients were identified as high risk on the basis of  $\geq 0.1$  mV of exercise-induced ST-segment depression and inability to complete stage I of the Bruce protocol. These patients had an average mortality rate of 5% per year. Patients who could exercise to at least stage III of the Bruce protocol without ST changes (34%) constituted the low-risk group (estimated annual mortality, less than 1%).<sup>123</sup>

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.<sup>152,271–273</sup>

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.<sup>152,272</sup> The DTS equals the exercise time in minutes minus (five times the ST-segment deviation, during or after exercise in millimetres) minus (four times the angina index, which has a value of '0' if there is no angina, '1' if angina occurs, and '2' if the angina is the reason for stopping the test (Figure 4). In the original description of this score in a population with suspected CAD, 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 (Figure 5).

**Stress echocardiography.** Stress echocardiography may also be used effectively to stratify patients according to their risk of subsequent cardiovascular events<sup>158,274</sup> and similarly has an excellent negative predictive value,<sup>275,276</sup> in patients with a negative test having a hard event rate (death or MI) of <0.5%/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.<sup>155</sup> Identification of a high risk cohort allows for appropriate further investigation and/or intervention.

**Stress perfusion scintigraphy.** SPECT perfusion scintigraphy is a useful method of non-invasive risk stratification, readily identifying those patients at greatest risk for subsequent death and MI. 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 MI of less than 1% per year, which is nearly as low as that of the general population.<sup>169,170,277</sup> The only exceptions would appear in patients with normal perfusion images with either a high-risk treadmill ECG score or severe resting LV dysfunction.<sup>278</sup>

In contrast, abnormal findings on stress perfusion scintigraphy have been associated with severe CAD, and

Duke treadmill score		
Exercise time in minutes		<i>n</i>
mm ST-depression × 5		– <i>n</i>
Angina, not limiting × 4		– <i>n</i>
Angina, limiting × 8		– <i>n</i>
Risk	1-year mortality	
Low risk	≥ 5	0.25%
Intermediate	4 to –10	1.25%
High	≤ –11	5.25%

Figure 4 Duke treadmill score.<sup>272</sup>

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 <sup>201</sup>Th, increased lung uptake<sup>279</sup> on post-exercise or pharmacological stress images are all adverse prognostic indicators.<sup>158,174,277,278</sup>

The results of planar and SPECT perfusion scintigraphy can be used to identify a 'high-risk' patient subset. These patients, who have a greater than 3% annual mortality rate, should be considered for early coronary arteriography, as their prognosis may be improved by revascularization. Exercise scintigraphy 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 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 where 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 ejection fraction (EF)

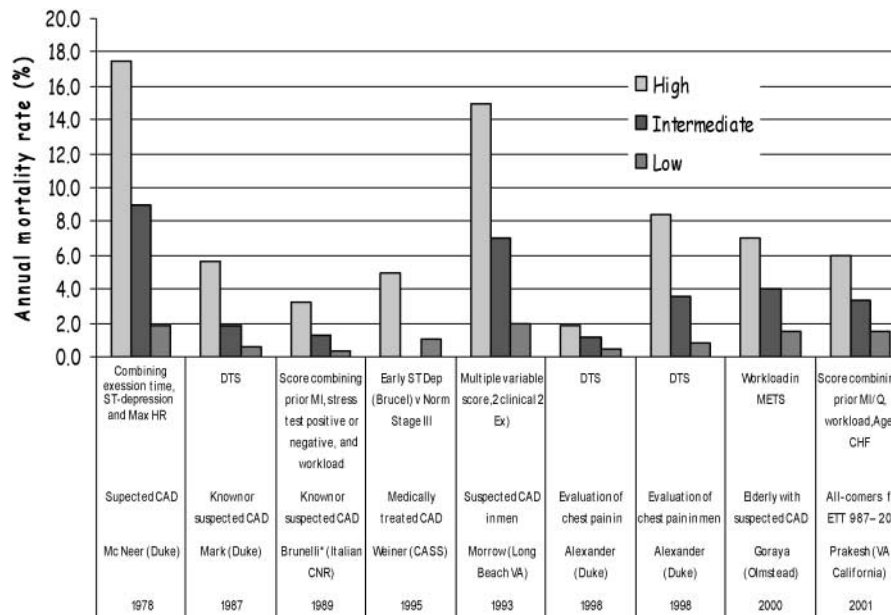


Figure 5 Prognostic stratification according to combined clinical and exercise variables.<sup>52,270-273,681-683</sup>

declines, mortality increases. A resting EF of less than 35% is associated with an annual mortality rate greater than 3% per year.<sup>67,123,124,280</sup>

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 EF >50% was 35–49%<sup>280</sup> 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.<sup>261</sup>

Ventricular function affords additional prognostic information to coronary anatomy, with reported 5-year survival rates of a man with stable angina and three-vessel disease ranging from 93% in those with normal ventricular function to 58% with reduced ventricular function.<sup>67</sup> Impaired ventricular function may be inferred from extensive Q-wave on ECG, symptoms or signs of heart failure, or measured non-invasively by echocardiography, radionuclide techniques or contrast ventriculography at the time of coronary arteriography.

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,<sup>281-283</sup> 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.<sup>284</sup> 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 patients,<sup>285</sup> and the European guidelines for the management of hypertension recommend an echocardiogram for patients with

hypertension.<sup>286</sup> 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.<sup>67,124,287,288</sup>

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 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 one-vessel disease, 59% for those with two vessel disease and 50% for those with three vessel disease ( $P < 0.001$ ).<sup>280</sup> Patients with severe stenosis of the LM coronary artery have a poor prognosis when treated medically. The presence of severe proximal left anterior descending artery (LAD) disease also significantly reduces the survival rate. The 5-year survival rate with three-vessel disease plus greater than 95% proximal LAD stenosis was reported to be 54% compared with a rate of 79% with three-vessel disease without LAD stenosis.<sup>288</sup> However, it should be appreciated that in these 'older' studies preventive therapy was not at the level of current recommendations regarding both lifestyle and drug therapy. Accordingly, absolute estimates of risk derived from these studies, in general, over-estimate the risk of future events.

Recent angiographic studies indicate that a direct correlation exists between the angiographic severity of coronary disease and the amount of angiographically insignificant plaques in the coronary tree.<sup>289</sup> The higher mortality rates in patients with multivessel disease may be a consequence of a higher number of mildly stenotic and non-stenotic plaques that are potential sites for acute coronary events than those with one-vessel disease.

The major focus in non-invasive risk stratification is on subsequent patient mortality, with the rationale to identify patients in whom coronary arteriography and subsequent revascularization might decrease mortality, that is those with three-vessel disease, LM CAD, and proximal anterior descending CAD.<sup>69,290</sup>

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 greater than 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 Classification (CCS), 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)

### Special diagnostic considerations: angina with 'normal' coronary arteries

The clinicopathological correlation of symptoms with coronary anatomy varies widely in angina from typical symptoms of angina due to significant coronary lesions causing transient ischaemia when myocardial demand is increased, to clearly non-cardiac chest pain with normal coronary arteries

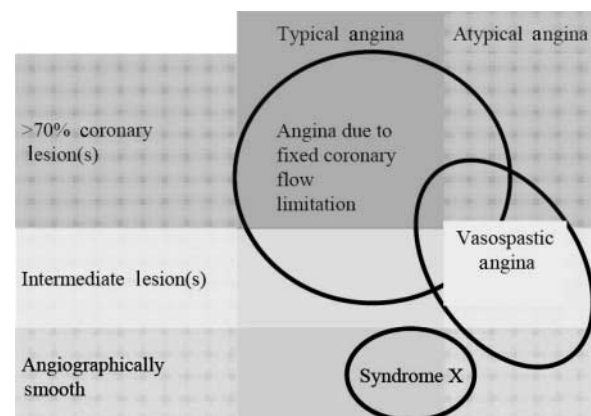


Figure 6 Schematic representation of clinico-pathological variants in angina.

on the other end of the spectrum. Spanning the extremes of this spectrum are a number of clinicopathological correlates which may overlap to a greater or lesser extent with each other (Figure 6). These range from atypical anginal symptoms with significant coronary stenoses, which would fall under the umbrella of the conventional diagnosis of angina pectoris, to typical anginal symptoms with angiographically normal coronary arteries which might be described as cardiac Syndrome X. Vasospastic angina, caused by dynamic coronary obstruction in coronary arteries which may be either angiographically smooth or significantly stenosed, is a further factor to be considered in the diagnosis. A considerable proportion of patients, especially women, who undergo coronary arteriography because of symptoms of chest pain do not have significant CAD.<sup>291</sup> In these patients, the features of chest pain may suggest one of the following three possibilities.

- Pain involves a small portion of the left hemithorax, lasts for several hours or even days, is not relieved by nitroglycerin, and may be provoked by palpation (non-anginal pain, often musculoskeletal in origin)
- Pain has typical features of angina in terms of location and duration but occurs predominantly at rest (atypical angina, which may be due to coronary spasm vasospastic angina)
- Angina with mostly typical features (although duration may be prolonged, and relation to exercise somewhat inconsistent) associated with abnormal results of stress tests (cardiac Syndrome X)

Detailed discussion of the management of the first group is beyond the scope of these guidelines. With regard to the 'atypical angina' group, in general this term refers to symptoms with any two of the three main features of typical angina pectoris as outlined in Table 2, and the term may be used interchangeably with 'probable angina'. Suspected vasospastic angina is a specific subgroup of atypical angina which is atypical only in that it lacks a consistent association with exercise. Other forms of atypical angina are not discussed separately, but a brief description of the diagnostic evaluation of cardiac Syndrome X and vasospastic angina are outlined below.

### Syndrome X

*Clinical picture.* Although there is no universally accepted definition of Syndrome X, to fulfil the classical description of 'Syndrome X'<sup>292</sup> 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.<sup>293</sup> Severe attacks of resting angina may prompt recurrent emergency presentations, and hospital admissions with an inaccurate diagnosis of unstable angina leading to inappropriate diagnostic and therapeutic procedures.

In a subset of patients with Syndrome X, microvascular dysfunction can be demonstrated and this entity is commonly referred to as 'microvascular angina'.<sup>294</sup>

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 dysfunction,<sup>295</sup> LVH, interstitial and perivascular fibrosis with diastolic dysfunction<sup>296</sup> changes in myocardial and coronary ultrastructure.<sup>297</sup> and reduced coronary flow reserve.<sup>298</sup> 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.<sup>299</sup>

*Pathogenesis.* The mechanism of chest pain in patients with angina despite a normal coronary angiogram continues to be controversial. Functional abnormalities of the coronary microcirculation during stress, including abnormal dilator responses and a heightened response to vasoconstrictors, have been considered potential mechanisms of chest pain and ischaemic-appearing ST-segment depression during exercise.<sup>300</sup> However, others failed to find haemodynamic or metabolic evidence of ischaemia in many patients with Syndrome X<sup>301</sup> but propose abnormal cardiac sensitivity (coupled with some impairment in coronary flow reserve) in these patients that may lead to chest pain on a non-ischaemic basis.<sup>302</sup>

*Prognosis.* Although the prognosis in terms of mortality of patients with Syndrome X appears to be favourable,<sup>303</sup> the morbidity of patients with Syndrome X is high<sup>304,305</sup> and the condition is frequently associated with continuing episodes of chest pain and hospital readmission.<sup>306</sup> There is emerging evidence that identification of impaired endothelial dysfunction in this patient population may identify a subgroup at risk for the future development of atherosclerotic coronary disease<sup>307</sup> and with a less benign prognosis than previously thought.<sup>305,308-310</sup>

*Diagnosis of Syndrome X.* Diagnosis and management of patients with chest pain and normal coronary arteries represent a complex challenge. 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 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

emphasized and the patient should be informed and reassured about the benign course of the condition.

### Recommendations for investigation in patients with 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)
- (2) Intracoronary ultrasound, coronary flow reserve, or FFR 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. Such pain characteristics are often caused by coronary artery spasm, especially when the pain occurs at night and in the early morning hours.<sup>311</sup> If the chest pain is severe, this may lead to hospital admission. Nitrates usually relieve the pain within minutes. The terms vasospastic or variant angina may be used to describe such symptoms, although 'Prinzmetal angina'<sup>312</sup> has also been used. This term was initially used to describe patients with clearly documented ST-elevation during chest pain due to coronary spasm. Angina at rest with preserved exercise tolerance may also be associated with significant obstructive coronary disease without demonstrable vasospasm, 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 vasospastic angina have obstructive coronary disease<sup>313</sup> and in such patients vasospastic angina may co-exist with typical exertional angina due to fixed coronary lesions. Non-exertional symptoms due to vasospasm may also occur in patients with minimal or no angiographically evident coronary disease, and typical exertional angina and dyspnoea may also occur in patients with vasospasm but entirely normal coronary arteries. This indicates some overlap with patients suffering from Syndrome X (Figure 6).<sup>314</sup> The prevalence of vasospastic angina is difficult to assess, not least because of its overlap with typical angina and Syndrome X. Vasospasm may occur in response to smoking, electrolyte disturbances (potassium, magnesium), cocaine use, cold stimulation, autoimmune diseases, hyperventilation or insulin resistance. There is also an ethnic pre-disposition, with a higher prevalence in Japanese populations.

*Pathogenesis.* The mechanisms leading to vasospastic angina are not entirely clear, but hyperreactivity of smooth muscle cells of the involved coronary segment<sup>315</sup> may play a role,

and endothelial dysfunction may also be involved.<sup>316,317</sup> The causes of smooth muscle cell hyperreactivity are unknown, but several possible contributing factors have been suggested, including increased cellular rho-kinase activity,<sup>318</sup> abnormalities in ATP-sensitive potassium channels,<sup>319</sup> and membrane Na<sup>+</sup>-H<sup>+</sup> countertransport.<sup>320</sup> Other contributing factors may be imbalances in the autonomic nervous system,<sup>321,322</sup> enhanced intracoronary concentrations of vasoconstricting substances, such as endothelin,<sup>323</sup> and hormonal changes, such as post-oophorectomy.<sup>324,325</sup>

*Natural history and prognosis.* The prognosis of vasospastic angina depends on the extent of underlying CAD. Death and MI are not frequent in patients without angiographically significant obstructive disease, but do occur.<sup>326</sup> Coronary death in the population with non-obstructive lesions has been reported as ~0.5% per annum,<sup>327,328</sup> but those with spasm superimposed on stenotic lesions do significantly less well.<sup>327,329–332</sup>

### Diagnosis of vasospastic angina

*Electrocardiography.* The ECG during vasospasm is classically described as showing ST-elevation.<sup>312</sup> In others, ST-depression can be documented,<sup>333</sup> whereas others may show no ST-segment shift at all.<sup>334,335</sup> However, as attacks tend to resolve quickly, 12-lead ECG documentation tends to be difficult. Repeated 24 h ECG monitoring may be able to capture ST-segment shifts associated with anginal symptoms in these patients.<sup>336</sup>

*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.<sup>337</sup> Hyperventilation and the cold pressor test have only a rather limited sensitivity for the detection of coronary spasm.<sup>338</sup> Thus, acetylcholine injections into the coronary artery<sup>339</sup> are used in most centres today, but intracoronary ergonovine provocation gives similar results.<sup>340,341</sup> Acetylcholine is injected in incremental doses of 10, 25, 50 and 100 µg separated by 5 min intervals. Intravenous ergonovine may also be used but may be associated with more diffuse spasm, which is not desirable.

Coronary spasm may be focal or diffuse.<sup>335</sup> Lumen reductions between 75 and 99% when compared with the diameter following nitroglycerin injection are defined as spasm in the literature,<sup>342,343</sup> whereas lumen reductions <30% are commonly seen in non-spastic coronary segments<sup>344</sup> and may represent the 'physiological' constrictor response to acetylcholine provocation.<sup>342</sup>

Acetylcholine or ergonovine provocation of coronary spasm is a safe test,<sup>341,345</sup> if the agent is infused selectively into each of the three major coronary arteries. Non-invasive intravenous ergonovine provocative testing has also been described with the addition of echocardiographic or perfusion scintigraphy to electrocardiographic monitoring increasing the sensitivity and specificity of these



tests.<sup>346,347</sup> However, invasive documentation of vasospasm remains the gold standard against which diagnostic tests are evaluated, and as fatal complications due to prolonged spasm involving multiple vessels may occur with intravenous injection of ergonovine,<sup>348</sup> the intracoronary route is preferred. 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 MI and death.* Efforts to prevent MI and death in coronary disease focus primarily on reducing the incidence of acute thrombotic events and the development of ventricular dysfunction. These aims are achieved by lifestyle or pharmacological interventions which (i) reduce plaque progression, (ii) stabilize plaque, by reducing inflammation and preserving endothelial function, and finally (iii) by preventing thrombosis if endothelial dysfunction or plaque rupture occur. In certain circumstances, such as in patients with severe lesions in coronary arteries supplying a large area of jeopardized 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 minimizing 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, and the implications of the diagnosis and the treatments that may be recommended. The patient can be reassured that, in most cases, both the symptoms of angina and prognosis can be improved with proper management. Comprehensive risk stratification should be conducted as outlined above, and 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<sup>250</sup> on Cardiovascular Disease Prevention in Clinical Practice should be followed.

### Treatment of the acute attack

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.

All preventive measures, pharmacological and non-pharmacological, described in this document apply similarly to men and women,<sup>349</sup> even if there is less documentation of health benefits among female compared with male patients with stable angina pectoris and the clinical presentation of the disease may differ between genders. Risk factors, clinical presentation, and the level of risk for serious cardiovascular complications should determine the need for preventive and therapeutic interventions, rather than the gender of the patient. Recommendations concerning hormone replacement therapy have changed and are commented upon subsequently.

### Smoking

Cigarette smoking should be strongly discouraged, as there is abundant evidence that it is the most important reversible risk factor in the genesis of coronary disease in many patients.<sup>350,351</sup> Cessation of smoking greatly improves both symptoms and prognosis. Patients often require special help in abandoning their addiction, and nicotine replacement therapy has proved effective and safe in helping patients with CAD to quit smoking.<sup>352–355</sup>

### Diet and alcohol

Dietary interventions are effective in the prevention of events in patients with established CAD, when properly implemented.<sup>1</sup> Certain food types are to be encouraged such as fruit, vegetables, cereal, and grain products as well as skimmed dairy products, fish, and lean meat, many of which are major components of the Mediterranean diet. Patients should thus be encouraged 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.<sup>356</sup> Those who are overweight should be put on a weight reducing diet.

Alcohol in moderation may be beneficial,<sup>357</sup> but excessive consumption is harmful, especially in patients with hypertension or heart failure. It has been difficult to develop public health recommendations on safe limits of alcohol use, but moderate alcohol consumption should not be discouraged.<sup>1,358–360</sup>

### Omega-3 fatty acids

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 (85% men) with a recent MI.<sup>361</sup> A detailed further analysis of the GISSI-Prevenzione trial<sup>362</sup> showed an early reduction of cardiovascular death which was dependent on fewer sudden deaths. The effect was attributed to antiarrhythmic effects of omega-3 fatty acid supplementation, in agreement with previous experimental data.<sup>362</sup> A meta-analysis of omega-3 fatty acid supplementation<sup>363</sup> confirmed the effect on sudden death and showed a reduction of mortality, but concluded that reasonably large risk reduction with such therapy can only be expected among high-risk patients, such as patients with a recent MI. A more recent meta-analysis of the effects of lipid-lowering therapies on mortality also confirmed the beneficial effect of n-3 fatty acids in secondary prevention.<sup>364</sup> Patients with stable angina without high risk features should rarely be considered for omega-3 fatty acid supplementation. Dietary intervention to achieve fish consumption at least once weekly can, however, be more widely recommended.<sup>365,366</sup>

### Vitamins and antioxidants

Vitamin supplementation has not been shown to reduce cardiovascular risk in patients with CAD. In contrast to the above-mentioned findings with dietary intervention, several large studies have failed to find benefits from pharmacological supplementation with antioxidant vitamins.<sup>367-369</sup>

### Hypertension, diabetes, and other disorders

Concomitant disorders should be managed appropriately. Particular attention should be given to control of elevated blood pressure, diabetes mellitus, and other features of the metabolic syndrome which increase the risk of progression of coronary disease. Of particular note, the Task Force report on CVD prevention<sup>250</sup> suggests considering a lower threshold for institution of pharmacological therapy for hypertension (130/85) for patients with established CHD (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 mm Hg.<sup>286</sup> Diabetes is a strong risk factor for cardiovascular complications and should be managed carefully with good glycaemic control and attention to other risk factors.<sup>286,370,371</sup>

Multifactorial intervention in diabetic patients may indeed reduce both cardiovascular and other diabetic complications markedly.<sup>372</sup> Recently, the addition of pioglitazone to other hypoglycaemic medication has been shown to reduce the incidence of death, non-fatal MI, or stroke (a secondary endpoint) in patients with type 2 diabetes and vascular disease by 16%; the primary composite endpoint, which included a number of vascular endpoints, was not significantly reduced.<sup>373</sup> Anaemia or hyperthyroidism, if present, should be corrected.

### Physical activity

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. Advice on exercise must take into account the

individual's overall fitness and the severity of symptoms. An exercise test can act as a guide to the level at which an exercise programme can be initiated. Detailed recommendations on exercise prescription and on recreational and vocational activities are provided by the ESC Working Group on Cardiac Rehabilitation.<sup>150</sup>

### Psychological factors

Although 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. Appropriate programmes may reduce the need for drugs and surgery.<sup>374</sup> A randomized controlled trial<sup>375</sup> of a self-management plan showed an apparent improvement in the psychological, symptomatic, and functional status of patients with newly diagnosed angina.

### Car driving

In most countries, patients with stable angina are permitted to drive except for commercial public transport or heavy vehicles. Stressful driving conditions should be avoided.

### Sexual intercourse

Sexual intercourse may trigger angina. Common sense will dictate that this should not be too physically or emotionally demanding. Nitroglycerin prior to intercourse may be helpful. Phosphodiesterase (PGE5) inhibitors such as sildenafil, tadalafil, and 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.<sup>376</sup> The patient must be informed about the potentially harmful interactions between PGE5 inhibitors and nitrates or NO (nitric oxide) donors.<sup>377,378</sup>

### Employment

An assessment should always be made of the physical and psychological factors involved in an affected subject's work (including housework). Patients should, if possible, be encouraged to continue in their occupation, with appropriate modifications, if necessary.

## Pharmacological treatment of stable angina pectoris

The goals of pharmacological treatment of stable angina pectoris are to improve quality of life by reducing the severity and/or frequency of symptoms and to improve the prognosis of the patient. Measures of quality of life reflect disease severity and carry prognostic information if properly assessed.<sup>379</sup> When selecting evidence-based strategies for pharmacological prevention of cardiac complications and death, one should consider the often benign prognosis of the patient with stable angina pectoris. Pharmacotherapy is a viable alternative to invasive strategies for the treatment of most patients with stable angina pectoris<sup>51,290,380,381</sup> and was actually associated with fewer complications than surgery or PCI during a 1-year follow-up of the MASS-II study.<sup>382</sup> An invasive treatment strategy may

be reserved for patients at high risk or patients with symptoms that are poorly controlled by medical treatment.<sup>290</sup> The intensity of preventive pharmacotherapy should be tailored to the individual risk of the patient, keeping in mind the relatively low risk of many patients with stable angina pectoris.

### Pharmacological therapy to improve prognosis

Co-existing disorders such as diabetes and/or hypertension in patients with stable angina should be well controlled, dyslipidaemia should be corrected, and smoking cessation attempted (without or with pharmacological support). Statin and angiotensin-converting enzyme (ACE)-inhibitor treatment may provide protection above that which can be ascribed to their lipid and blood pressure lowering effects, respectively, and are discussed separately. In addition, antiplatelet treatment should always be considered for patients with ischaemic heart disease. Levels of evidence based on prognosis and symptom relief are provided for the recommended treatments for angina in the treatment algorithm illustrated in *Figure 7*.

**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, whereas clopidogrel may be considered for some patients. Because of the evolving story of increased cardiovascular risks with cyclooxygenase (COX)-2 inhibitor or NSAID treatment, as well as interactions between NSAIDs and aspirin, these drugs will also be commented upon from the cardiovascular perspective.

**Low-dose aspirin.** Aspirin remains the cornerstone of pharmacological prevention of arterial thrombosis and is very well studied.<sup>383–387</sup> Aspirin acts via irreversible inhibition of platelet COX-1 and thus thromboxane production, which is normally complete with chronic dosing  $\geq 75$  mg/day.<sup>385</sup> 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.<sup>387</sup> In agreement with this interpretation, an observational *post hoc* analysis of the CURE study found an increased risk of cardiovascular events with an aspirin dosage  $\geq 200$  vs.  $\leq 100$  mg per day (HR 1.23; 95% CI 1.08–1.39) in patients with acute coronary syndromes.<sup>388</sup> Randomized studies comparing different dosages of aspirin are, however, few.

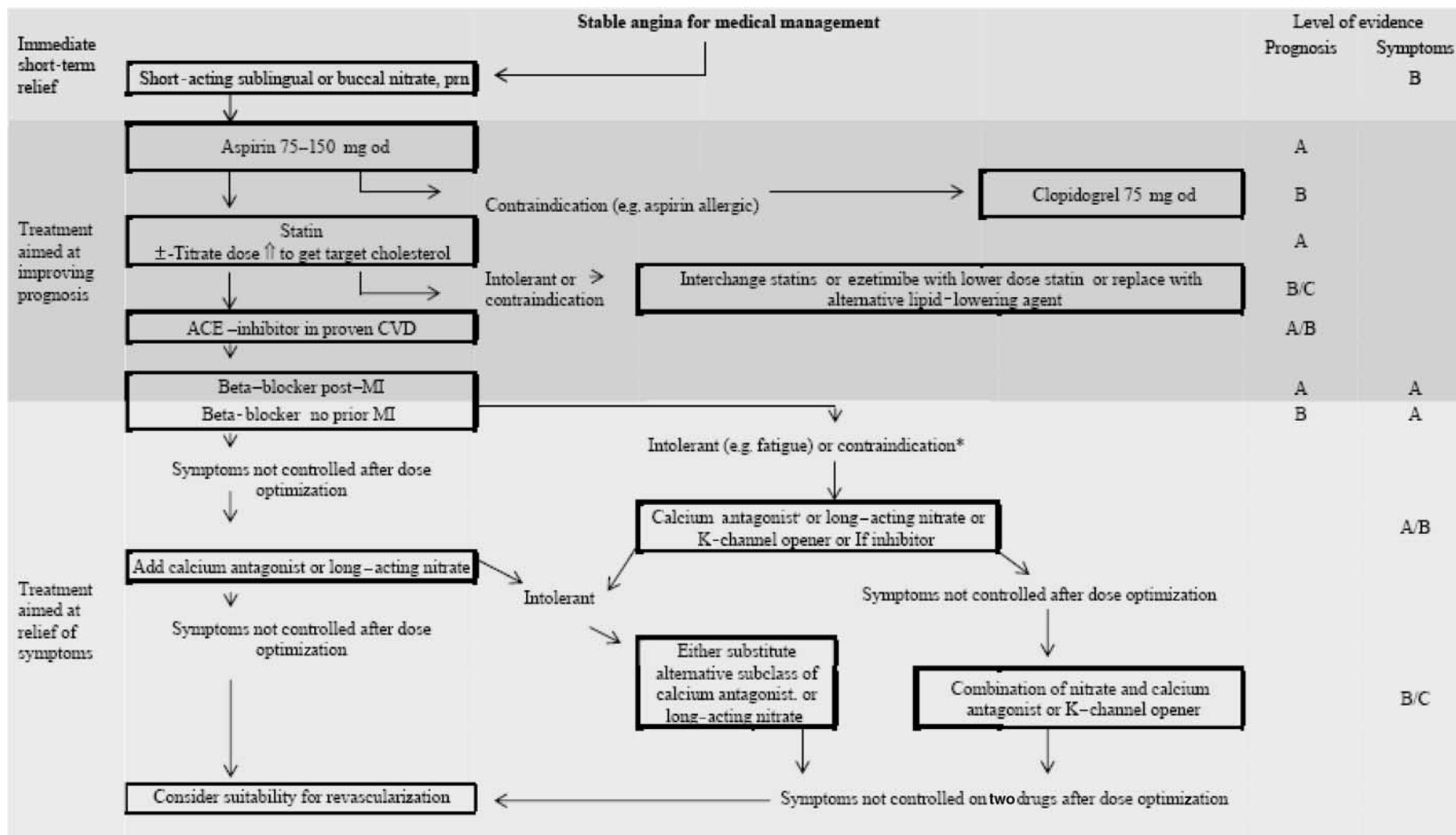
Contrary to the antiplatelet effects, the gastrointestinal side-effects of aspirin increase at higher doses.<sup>385</sup> In a well-conducted observational study, a doubling of peptic ulcer bleeding was observed when the aspirin dose increased from 75 to 160 mg, and another doubling when it increased to 325 mg/day.<sup>389</sup> However, in a meta-analysis of long-term studies,<sup>390</sup> there was no clear dose–response relationship between studies regarding the risk of gastrointestinal haemorrhage. The incidence of gastrointestinal haemorrhage was 2.30% with aspirin at a dosage below 162.5 mg/day vs. 1.45% with placebo, relative risk 1.59 (95% CI 1.40–1.81). The relative risk in trials using higher doses ( $> 162.5$  mg) was 1.96 (95% CI 1.58–2.43). In this meta-analysis, the large US Physicians Health Study (USPHS) with 325 mg on alternate days dominated the low-dose aspirin group, whereas the The Swedish Angina Pectoris Aspirin Trial

(SAPAT) study (75 mg daily) was not included. Variable definitions and reporting of gastrointestinal bleeds may confound between-study comparisons of different dosages of aspirin. Antiplatelet therapy in patients with upper gastrointestinal bleeding problems is commented upon after clopidogrel.

Intracranial bleeds may increase with all antithrombotic drugs. The relative risk of suffering an intracranial haemorrhage increases by 30%,<sup>391</sup> 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  $\geq 75$  mg/day.<sup>383,385</sup> 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.<sup>383,385</sup> 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.

SAPAT showed a 34% reduction of MI or cardiac death, corresponding to an absolute risk reduction (ARR) of 1% per year, with aspirin 75 mg/day compared with placebo in sotalol-treated patients with stable angina pectoris.<sup>47</sup> Low-dose aspirin treatment slightly increased the risk of major gastrointestinal haemorrhage (11 vs. 6 cases during more than 4000 patient-years of treatment in each group). Treatment was discontinued due to adverse effects in 109 aspirin vs. 100 placebo-treated patients.<sup>47</sup> Thus, aspirin 75 mg/day is both effective and well tolerated in stable angina pectoris. Treatment of a small subgroup of doctors with angina pectoris with 325 mg aspirin every other day (compared with placebo) resulted in a significant reduction of non-fatal MI in the USPHS.<sup>392</sup> Low daily dosing of aspirin (75 mg) is thus well documented in stable angina pectoris and is preferred in order to increase compliance (with a regular daily medication routine) and to reduce risks of side-effects and interactions.

**COX-2 inhibitors and NSAIDs.** 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.<sup>393</sup> 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.<sup>394</sup> An increased risk of suffering fatal or non-fatal MI was also found in a meta-analysis of other randomized trials with rofecoxib.<sup>395</sup> There is also supporting evidence for harmful effects of COX-2 inhibition from several observational studies.<sup>396</sup> A cancer prevention trial with celecoxib showed a dose-related increase in the risk of suffering cardiovascular complications, with HRs of 2.3 (95% CI 0.9–5.5) and 3.4 (1.4–7.8) for 200 and 400 mg celecoxib bid, respectively.<sup>397</sup> A placebo-controlled study of parecoxib/valdecoxib (iv + oral therapy) for the treatment of post-operative pain after CABG showed an increased risk of suffering cardiovascular events with only 10 days of treatment with COX-2 inhibition.<sup>398</sup> 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



**Figure 7** Algorithm for medical management of stable angina. High-risk candidates for revascularization on prognostic grounds alone should be identified and referred appropriately. (Asterisk) Relative contraindications to beta-blockade include asthma, symptomatic peripheral vascular disease, and first-degree heart block. (Double dagger) 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 need for revascularization and hospitalization for chest pain.

risk. In addition, COX-2 inhibition increases the risk of suffering stroke, heart failure, and hypertension.<sup>399</sup> 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 (NSAIDs) can inhibit thromboxane production and platelet aggregation,<sup>400,401</sup> as demonstrated for naproxen.<sup>402</sup> However, the reversible NSAIDs rarely inhibit thromboxane production as effectively as aspirin,<sup>385</sup> and it has been shown that <5% residual COX-1 activity in platelets is sufficient to sustain full platelet aggregation.<sup>403</sup> Cardioprotective effects of naproxen treatment have been discussed,<sup>404–407</sup> but the balance of evidence indicates that also non-selective NSAIDs may increase the risk of cardiovascular complications.<sup>396</sup> It is recommended to primarily use paracetamol. If NSAIDs are needed, they should be used in the lowest effective doses and for the shortest possible duration. A warning has also recently been issued by the FDA for naproxen.<sup>408</sup> 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, as this NSAID prevents aspirin from irreversibly acetylating the COX-1 enzyme of platelets, as may naproxen.<sup>409,410</sup> Diclofenac is a relatively COX2-selective NSAID and, therefore, a poor platelet inhibitor, but does not interfere with the antiplatelet effects of aspirin and may be used in combination with aspirin.<sup>411</sup>

**Clopidogrel.** Clopidogrel and ticlopidine are thienopyridines which act as non-competitive ADP receptor antagonists and which have antithrombotic effects similar to aspirin.<sup>385</sup> Ticlopidine efficacy has mainly been documented in stroke and PCI<sup>385,387</sup> and has been replaced by clopidogrel due to the risk of neutropenia and thrombocytopenia and more symptomatic side-effects with ticlopidine. The main study documenting clopidogrel use in stable CAD is CAPRIE,<sup>412</sup> which included three equally large groups of patients with previous MI, previous stroke, or peripheral vascular disease (PVD).<sup>412</sup> When compared with aspirin 325 mg/day, which may be less effective than 75 mg/day (see *Figure 7* in Collaborative Meta-analysis of Randomized Trials<sup>387</sup>), clopidogrel 75 mg/day was slightly more effective (ARR 0.51% per year;  $P = 0.043$ ) in preventing cardiovascular complications in high-risk patients.<sup>412</sup> When comparing outcomes in the three subgroups of patients enrolled in CAPRIE, the benefit with clopidogrel appeared in the PVD subgroup only.<sup>412</sup> Gastrointestinal haemorrhage was only slightly less common with clopidogrel compared with aspirin treatment (1.99 vs. 2.66% during 1.9 years of treatment), despite the relatively high aspirin dose.<sup>412</sup> The benefit of clopidogrel may have been over-estimated because the dose of aspirin with which it was compared (325 mg) may not be the most effective dose. The CAPRIE study did not include patients with aspirin intolerance, and we do not know the risk of gastrointestinal bleeding during clopidogrel compared with placebo treatment. Clopidogrel is 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 (discussed subsequently). After coronary stenting, an acute coronary syndrome, or an ST-elevation MI, clopidogrel may be

combined with aspirin during a finite period of time, but combination therapy is currently not warranted in stable angina pectoris. Clopidogrel treatment increases the risk of severe bleeding in connection with CABG surgery.<sup>413</sup>

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. A study by Lau *et al.*<sup>414</sup> showed that atorvastatin, but not pravastatin, dose-dependently inhibited the effect of clopidogrel on ADP-mediated platelet activation. The study also showed the expected interactions between clopidogrel and antibiotics that inhibit (erythromycin and troleandomycin) or induce (rifampicin) CYP3A4.<sup>414</sup> Another study with clopidogrel maintenance treatment found no interaction with low-dose atorvastatin (10 mg daily) treatment.<sup>415</sup> The short-term effects of a 300 mg loading dose of clopidogrel in connection with PCI may<sup>416</sup> or may not<sup>417</sup> be attenuated by co-treatment with lipophilic statins (atorvastatin, simvastatin, and lovastatin). The effects of a 600 mg loading dose appear to be unaffected by treatment with atorvastatin or simvastatin.<sup>418,419</sup> Observational *post hoc* analyses of outcomes among patients receiving maintenance co-treatment with clopidogrel and interacting statin have not shown differences in outcome, but there are no properly designed prospective studies that address the issue. Data from the large GRACE registry indicate that statin treatment has additional benefit to those of clopidogrel treatment, as might be expected.<sup>420</sup> Thus, the literature on statin–clopidogrel interactions is inconsistent, and the importance of interactions between maintenance therapy with lipophilic statins and clopidogrel is at present not known.

**Antiplatelet therapy in patients with gastrointestinal intolerance to aspirin.** Gastrointestinal haemorrhages may increase with any antiplatelet treatment, but the size of this effect with clopidogrel is not known in the absence of data from placebo-controlled trials. It has been speculated that antiplatelet treatment interferes with the normal wound healing process which limits the progression of sub-clinical and rather common (2% per month without any treatment) gastric erosions, due to reduced release of platelet stored growth factors such as VEGF.<sup>421</sup> In addition, aspirin causes dose-related gastric mucosal damage which may increase the incidence and severity of erosions. Upper gastrointestinal bleeding due to aspirin or NSAID therapy may be alleviated by inhibiting gastric acid secretion. Eradication of *Helicobacter pylori* infection, if present, also reduces the risk of aspirin-related gastrointestinal bleeding.<sup>422</sup>

Among the different acid reducing therapies available, proton pump inhibitor (PPI) treatment has been best documented. Thus, 30 mg/day of lansoprazole reduced the recurrence of ulcer complications from 14.8% in the placebo group to 1.6% ( $P = 0.008$ ) during a 12-month follow-up of gastroduodenal ulcer patients treated with 100 mg aspirin after *H. pylori* eradication.<sup>423</sup> A recent study showed that the addition of a PPI (esomeprazole 40 mg/day) 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.<sup>424</sup>

**Dipyridamole and anticoagulants.** Dipyridamole is not recommended for antithrombotic treatment in stable angina due to poor antithrombotic efficacy<sup>387</sup> and the risk of

worsening anginal symptoms due to coronary steal phenomena.<sup>425</sup> Anticoagulant drugs (warfarin or thrombin inhibitors), which are an alternative or combined with aspirin in certain high-risk patients, such as post-MI, are not indicated in the general stable angina population without a separate indication such as AF.

**Aspirin resistance.** Possible problems related to 'aspirin resistance' are of considerable interest<sup>386,426</sup> and have been much discussed. However, the phenomenon is ill-defined and may be characterized by the occurrence of cardiovascular events despite therapy (i.e. therapeutic failure) or by resistance to the pharmacological effects of aspirin, as determined by various laboratory methods. There is currently no 'gold standard' with which to evaluate aspirin resistance, and further research is needed before conclusions can be drawn and management schemes can be implemented.<sup>385</sup> Thus, aspirin resistance is still a matter for research on how to monitor and manage patients with insufficient responses to aspirin.<sup>427</sup> A similar issue with 'clopidogrel resistance' is emerging, and it is similarly unclear how this should be handled.<sup>428–430</sup>

**Lipid-lowering drugs.** Statin treatment reduces the risk of atherosclerotic cardiovascular complications in both primary and secondary prevention settings.<sup>431</sup> In patients with atherosclerotic vascular disease, simvastatin<sup>432</sup> and pravastatin<sup>433,434</sup> reduce the incidence of serious cardiovascular complications by some 30%. The Heart Protection Study (HPS)<sup>435</sup> and the Prospective Pravastatin Pooling Project (PPPP), which included primary prevention,<sup>433</sup> were large enough to show reduced mortality. Subgroup analyses indicate beneficial effects also in diabetic patients with vascular disease<sup>436,437</sup> and benefits of statin therapy have also been demonstrated in the elderly (>70 years).<sup>435,438</sup> In diabetic patients without manifest vascular disease, simvastatin 40 mg/day<sup>437</sup> and atorvastatin 10 mg/day<sup>439</sup> 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)<sup>440</sup> which evaluated atorvastatin treatment in the primary prevention of CHD in hypertensive patients with total cholesterol levels  $\leq 6.5$  mmol/L. In addition to the relatively low cholesterol levels, blood pressure control in the study was excellent, resulting in a low absolute risk of cardiac death and MI in this patient population. Hence, although the relative risk reduction in total coronary events was 36%, the ARR with statin treatment was only 0.34% per year regarding cardiac death or MI.<sup>440</sup> 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,<sup>431</sup> but mechanisms other than cholesterol synthesis inhibition, such as anti-inflammatory and antithrombotic effects,<sup>441–444</sup> may contribute to the cardiovascular risk reduction. In patients with stable angina, it has been shown that 7 days pre-treatment with atorvastatin 40 mg/day compared with placebo before PCI reduced procedural myocardial injury, as assessed by biochemical markers.<sup>445</sup> 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 pre-treatment levels of serum cholesterol, even in the 'normal' range.<sup>433,435,439</sup> 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). As for blood pressure (discussed subsequently), the risk associated with cholesterol increases log-linearly from low normal levels,<sup>431</sup> and it is therefore difficult to evaluate the relative importances of cholesterol lowering and other effects of statin treatment for the treatment benefits observed. A recent meta-analysis of the effects of different lipid-lowering therapies on mortality concluded that statins and n-3 fatty acids reduced mortality, whereas fibrates, resins, niacin, and dietary interventions failed to do so; a tendency towards reduced cardiac mortality was counterbalanced by an increase in non-cardiac mortality in the fibrate trials.<sup>364</sup>

Current European Prevention guidelines suggest a target value of <4.5 mmol/L (175 mg/dL) for total cholesterol 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, several studies have shown that C-reactive protein levels predict beneficial outcomes during statin therapy as well do cholesterol levels and that these two markers of statin responsiveness are additive.<sup>444</sup> Such analyses of clinical trial data suggest that cholesterol-independent effects of statin therapy may be of clinical importance. Thus, patient selection based on cholesterol levels and 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.<sup>446</sup> Therapy should aim at statin dosages documented to reduce morbidity/mortality in clinical trials. If this dose is not sufficient to achieve the target total cholesterol 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 or simvastatin  $\sim 24$  mg in patients with stable CAD.<sup>447,448</sup> 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.<sup>447</sup> 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 be also 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.<sup>449</sup> Effects on morbidity and mortality of

such combination treatment have, however, not yet been documented.

Lipid-modifying drugs other than statins, e.g. fibrates, resins, or 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.<sup>431,450,451</sup> However, benefits of gemfibrozil treatment in the VA-HIT study were primarily found among men with insulin resistance.<sup>452</sup> The combination of fibrates with statin therapy increases the risk of associated myopathy, but fenofibrate has been recently shown not to interfere with the catabolism of statins and is therefore less likely to increase the risk of myopathy when combined with moderate doses of statins.<sup>453,454</sup> Fibrate therapy was not associated with reduced total deaths in the meta-analysis of Studer *et al.*<sup>364</sup> Similarly, the recently published FIELD trial, comparing fenofibrate and placebo in 9795 patients with type 2 diabetes, found no mortality benefit and no significant reduction of the primary combined endpoint of coronary death and non-fatal MI.<sup>455</sup> Thus, gemfibrozil treatment may be considered in high-risk patients with low HDL cholesterol, but there is little support for a more widespread use of fibrates. Torcetrapib is a new agent which has been shown to raise HDL effectively,<sup>456</sup> but as yet there is insufficient evidence to make universal recommendations regarding target HDL or triglyceride levels to be achieved by pharmacotherapy in the general population with angina.

However, adjunctive therapy to statin therapy may be considered on an individualized basis in patients who have severe dyslipidaemia and remain at high risk after conventional measures (estimated cardiovascular mortality >2% per annum).

**ACE-inhibitors.** ACE-inhibitors are well established for the treatment of hypertension and heart failure, but have not been shown to confer better overall protection against the cardiovascular complications in hypertension, compared with that afforded by other antihypertensive drugs.<sup>457–459</sup> ACE-inhibitors or angiotensin receptor blockers (ARBs) are recommended for the treatment of diabetic patients with microalbuminuria to prevent progression of renal dysfunction, and as first-line agents to treat blood pressure in diabetic patients.<sup>286,370</sup>

Because of observed reductions in MI 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.<sup>252,460,461</sup> The HOPE study included high-risk patients with established CVD (coronary or non-coronary) or diabetes, and at least one other risk factor, and randomized them to treatment with ramipril or placebo for 5 years.<sup>460</sup> The EUROPA study included patients with stable CAD, with a broad range of risk but without clinical heart failure, who were randomized to treatment with perindopril or placebo for 4.2 years.<sup>461</sup> The PEACE study included patients with stable CAD without heart failure who were treated with trandolapril or placebo for 4.8 years.<sup>252</sup> As shown in *Figure 1*, the annual cardiovascular mortality rates in the placebo groups ranged from 0.8% (PEACE) to 1.6% (HOPE). The differences in cardiovascular risk were associated with differences in therapy at baseline.

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. Regarding reduction of the risk for cardiovascular death, HOPE reported a relative risk reduction of 26% (95% CI 13–36), EUROPA 14% (95% CI –3 to 28), and PEACE 5% (95% CI –19 to 24). The greatest relative risk reduction in HOPE was seen for stroke (RR 0.68; 95% CI 0.56–0.84), which was not reported in EUROPA but tended to be reduced in PEACE (HR 0.76; 95% CI 0.56–1.04). The PEACE investigators also reported no risk reduction when using the combined endpoints of HOPE (RR 0.93; 95% CI 0.81–1.07) and EUROPA (RR 0.96; 95% CI 0.83–1.12), respectively.<sup>252</sup> All three studies reported significant reductions of heart failure with ACE-inhibitor treatment.

Treatment benefits with ACE-inhibition were thus smaller in PEACE than in HOPE or EUROPA. One possible explanation for this difference in outcomes might be differences between the three ACE-inhibitors and/or the relative dosages used. However, the dosage of trandolapril used in PEACE was associated with a significant 25% reduction of cardiovascular death and a 29% reduction of severe heart failure, but a lesser decrease in non-fatal MI (–14%, NS) in consecutively enrolled post-MI patients with LV dysfunction in the TRACE study.<sup>462</sup> Baseline blood pressure was lower (133/78 mmHg) in the PEACE population than in either of the other two studies. The rates of previous revascularization ranged from 44% (HOPE) to 72% (PEACE), and drug therapy at baseline differed between the studies. Lipid-lowering therapy was received by only 29% of patients in HOPE compared with 70% in PEACE; the corresponding figures were 76 vs. 96% for antithrombotic drug treatment and 40 vs. 60% for beta-blocker use. Conversely, calcium channel blocker (CCB) use at baseline was more common in the HOPE study. Overall, PEACE patients were at lower absolute risk of cardiovascular death 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 ARR was greater in the population at highest absolute risk (MICRO-HOPE).<sup>463</sup> Pre-defined subgroup analysis of EUROPA and HOPE according to individual factors known to affect risk, such as age, diabetes, prior MI, non coronary vascular disease, and microalbuminuria, showed relative benefit of similar magnitude from therapy with ACE-inhibitor in almost all subgroups.

The blood pressure lowering effects of ACE-inhibition may have contributed to the beneficial results observed in HOPE and EUROPA. In HOPE, uncontrolled hypertension was an exclusion criterion and mean BP at entry was 139/79 mmHg.<sup>460</sup> The overall 3/2 mmHg blood pressure difference between ramipril and placebo treatment<sup>460</sup> may have been underestimated because of evening dosing of ramipril and office blood pressure measurements the next day. A HOPE substudy with 24 h ambulatory measurements reported a 10/4 mmHg blood pressure difference during

24 h and a 17/8 mmHg difference during the night, compared with 8/2 mmHg with office measurements in the same study.<sup>464</sup> In EUROPA, patients with uncontrolled hypertension (>180/100 mmHg) were also excluded, and the mean blood pressure at baseline was 137/82 mmHg. The overall blood pressure difference between perindopril and placebo treatment was 5/2 mmHg,<sup>461</sup> but larger differences may have occurred in subgroups of patients. However, analysis of the effect of treatment according to tertiles or quartiles of baseline blood pressure or fall in blood pressure on treatment shows significant benefit in all groups, even those in the lowest baseline blood pressure or smallest reduction in blood pressure with treatment.<sup>465</sup> Benefits of blood pressure reductions may be expected in subgroups of patients with clearly elevated blood pressure, but lowering blood pressure is associated with a lowering of cardiovascular risk also in the 'normal' range.<sup>466</sup> Thus, it is difficult to separate blood pressure-related effects from blood pressure-independent protection afforded by ACE-inhibition in stable angina pectoris.

Further clues regarding the effect of blood pressure lowering and ACE-inhibition in stable coronary disease may be obtained from the CAMELOT trial.<sup>467</sup> In this study, patients with angiographic evidence of coronary disease, although not necessarily obstructive, and normal blood pressure (mean BP 129/78 mmHg) were randomized to amlodipine, enalapril, or placebo and followed-up for 2 years. Sixty percent of the patients had hypertension and they were well treated in other respects (83% on statins, 75% on a beta-blocker, and 95% on aspirin). Blood pressure reductions (5 mm/2 mm) were almost identical in the two active treatment groups. The study was not powered to show effects on 'hard' endpoints ( $\approx$ 670 patients per group), but a 'post hoc' analysis of the combined endpoint of cardiovascular death, stroke, and MI showed similar non-significant relative risk reductions with enalapril (29%) and amlodipine (30%). Furthermore, an IVUS substudy in 274 patients showed a significant correlation between the progression of atheroma and the reduction in blood pressure even at this 'normal' range of blood pressure. The recently presented VALUE study, which compared antihypertensive treatment with amlodipine or valsartan in 15 245 patients (46% of whom had CAD) during 4.2 years, found that blood pressure lowering was more important than the type of drug used.<sup>468</sup> These studies support the contention that the benefits of lowering blood pressure extend into the 'normal' blood pressure range, as suggested by epidemiological data,<sup>466</sup> and that effects on outcome of blood pressure lowering are similar with ACE-inhibitors or ARBs when compared with calcium antagonists.<sup>457,458</sup> A report from the ASCOT study claims that blood pressure alone does not account for differences in outcome between different blood pressure treatment regimens, with the combination of CCBs and ACE-inhibitor therapy achieving greater reduction in clinical events than the combination of beta-blocker and diuretic.<sup>469</sup> However, the accompanying editorial points out that blood pressure differences may fully explain the differences in outcome between the two groups.<sup>470</sup> The benefits of blood pressure lowering in the normal range, are likely to be greatest in those at highest absolute risk,<sup>471</sup> particularly those with established vascular disease, but the level of blood pressure below which clinically appreciable benefit may be observed has not been established.

The blood pressure lowering effects of ramipril and perindopril compared with placebo, thus probably contributed to the risk reduction in the HOPE and EUROPA studies, but additional cardioprotection may also be afforded by ACE-inhibitors.<sup>441</sup> Furthermore, ACE-inhibition is well established in the treatment of heart failure or LV dysfunction,<sup>472</sup> and in the treatment of diabetic patients with renal involvement.<sup>370</sup> 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, or post-MI. In angina patients, without co-existing indications for ACE-inhibitor treatment the anticipated benefit of treatment (possible ARR) should be weighed against costs and risks for side-effects, and the dose and agent used of proven efficacy for this indication.

Effects of ARB treatment on prognosis in ischaemic heart disease are less well studied, but the VALIANT study showed similar effects of valsartan and captopril treatment in post-MI patients with heart failure.<sup>473</sup> However, the CHARM-preserved study<sup>474</sup> showed no significant benefit of candesartan compared with placebo in patients with preserved ventricular function. Thus, ARB treatment may be appropriate therapy for the treatment of heart failure, hypertension, or diabetic renal dysfunction in patients with angina when ACE-inhibition is indicated but not tolerated, but there is no indication for ARB therapy in patients with preserved ventricular function without diabetes as a secondary preventive agent.

*Hormone replacement therapy.* Epidemiological evidence suggested substantial cardiovascular benefits of postmenopausal use of hormone replacement therapy (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<sup>475,476</sup> and that there is an increased risk of developing CVD in primary prevention, and also an increased risk of suffering breast cancer.<sup>477</sup> Primary prevention with unopposed oestrogen therapy in hysterectomized women offered no cardiovascular protection.<sup>478</sup> New guidelines therefore recommend against routine use of HRT for chronic conditions<sup>349</sup> and current users have been advised to taper doses downwards towards discontinuation.<sup>479</sup>

*Beta-blockers.* The risk of suffering cardiovascular death or MI was reduced by beta-blockers by some 30% in post-MI trials.<sup>480</sup> 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 risk reduction in mortality with long-term secondary preventive treatment.<sup>481</sup> 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.<sup>481</sup> Also, a recent meta-analysis of atenolol trials in hypertension questioned the prognostic benefit afforded by this drug<sup>482</sup> even though beta-blockers as a group provided similar protection as other antihypertensive drugs in previous meta-analyses.<sup>457,458</sup> 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<sup>49</sup> and TIBET<sup>48</sup> studies, did not include placebo groups due to concerns about withholding symptomatic treatment during long periods of time. In the APSIS trial, which comprised 809 patients with clinically diagnosed stable angina pectoris, and a median follow-up of 3.4 years (>1400 patient-years of treatment in each group)<sup>49</sup> treatment with verapamil SR (240–480 mg/day) was associated with a similar cardiovascular event rate as treatment with metoprolol CR (100–200 mg/day). An extended follow-up of the APSIS study (to a median of 9.1 years) did not alter these findings, and showed an excellent prognosis of the stable angina patients, especially female patients without diabetes, compared with their background population.<sup>483</sup> In the TIBET trial, which comprised 682 patients with exercise-induced angina pectoris followed during a median of 2 years ( $\approx$ 450 patient-years in each group),<sup>48</sup> the effects of nifedipine SR (20–40 mg bid) did not differ significantly from those of atenolol (50 mg bid), but combination of the two drugs tended to be advantageous.

A smaller study ( $\approx$ 300 patient-years) in patients with CAD and 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.<sup>484</sup> 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.<sup>485,486</sup> Carvedilol, a non-selective beta-blocker that also blocks alpha-1 receptors, also reduces risk of death and hospitalizations for cardiovascular causes in patients with heart failure.<sup>487</sup>

**Calcium channel blockers.** Heart rate lowering CCBs may improve the prognosis of post-MI patients, as shown in the DAVIT II study for verapamil<sup>488</sup> and in a subgroup analysis of patients without signs of heart failure in the MDPIT study for diltiazem.<sup>489</sup> Also, in the INTERCEPT trial there was a trend towards a reduction in the primary endpoint of cardiac death, non-fatal re-infarction and refractory ischaemia, and a significant reduction of the need for revascularization among post-MI patients treated with diltiazem compared with placebo.<sup>490</sup> CCBs are also effective antihypertensive agents without advantages over other blood pressure lowering drugs regarding clinical outcomes overall, but CCB treatment is associated with an increased risk of heart failure.<sup>457–459</sup>

Prognostic documentation in stable CAD has not been available for dihydropyridine CCBs until recently. 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.<sup>491</sup> This sparked an intense 'calcium antagonist debate' which pointed out the inappropriateness of treatment with short-

acting vasodilator drugs such as dihydropyridine CCBs. A meta-analysis of the safety of nifedipine in stable angina pectoris suggested that the drug was safe.<sup>492</sup>

The recently published ACTION trial<sup>493</sup> (Table 5), which compared treatment with long-acting nifedipine and placebo during 4.9 years of follow-up in 7665 patients with stable angina pectoris, is adequately powered for assessments of morbidity and mortality. The ACTION trial showed no benefit of treatment with long-acting nifedipine 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,<sup>493</sup> but has not been shown to have beneficial effects on hard endpoints such as death and MI.

A major drawback with the ACTION trial is the liberal inclusion of patients with high blood pressure, as the blood pressure lowering effects of nifedipine compared with placebo would be expected to provide health benefits unrelated (or in addition) to those possibly afforded by the anti-ischaemic or other effects of calcium antagonism. Thus, ACTION included patients with blood pressures <200/105 mmHg, and 52% of the patients had blood pressures  $\geq$ 140/90 mmHg at baseline, even though the average blood pressure was 137/80 mmHg. The proportion with blood pressure  $\geq$ 140/90 mmHg was reduced to 35% in the nifedipine group and 47% in the placebo group,<sup>493</sup> indicating that attempts to achieve similar blood pressure control among all participants in the study were insufficient. On average, nifedipine treatment caused a slight, but significant and sustained elevation of heart rate by approximately 1 bpm, and reduced blood pressure by  $\sim$ 6/3 mmHg. Subgroup analysis of the ACTION study showed significant benefit of nifedipine treatment among patients with elevated blood pressure at baseline but a tendency towards unfavourable results among those who had blood pressures below 140/90 mmHg. A 6 mmHg reduction of systolic blood pressure would be expected to reduce major cardiovascular events by some 25% according to the meta-regression analysis of Staessen *et al.*,<sup>458</sup> and this effect should not be restricted to clearly hypertensive patients.<sup>466</sup> Thus, the findings of ACTION may not be compatible with the benefits one might expect due to the reduction of blood pressure.

The CAMELOT study<sup>467</sup> compared treatment with amlodipine, enalapril, or placebo in 1991 patients with stable CAD and normal blood pressure during 2 years of follow-up. As discussed earlier, amlodipine and enalapril treatment lowered blood pressure equally and seemed to reduce the incidence of 'hard' endpoints similarly, although these results were not significant.

The abovementioned APSIS<sup>49</sup> and TIBET<sup>48</sup> studies were not placebo-controlled or 'powered' to determine effects on mortality, but show no major differences between beta-blockers and CCBs with regard to cardiovascular morbidity and mortality during long-term treatment of stable angina pectoris. A meta-analysis of 72 trials comparing calcium antagonists and beta-blockers in stable angina pectoris indicated similar outcomes with the two drug classes.<sup>494</sup>

However, the mean duration of the studies in this meta-analysis was only 8 weeks. A meta-analysis restricted to six larger trials reached a similar conclusion.<sup>157</sup>

To conclude, there is no evidence to support the use of CCBs for prognostic reasons in uncomplicated stable angina, although heart rate lowering CCBs may be used as an alternative to beta-blockers post-MI 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 (i.e. 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 (e.g. 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)
- (2) Fibrate or nicotinic acid as adjunctive therapy to statin in patients with low HDL and high triglycerides at high risk (>2% annual CV mortality) (level of evidence C)

#### 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'.<sup>157,377,495,496</sup> 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.

There is marked first-pass metabolism of orally administered nitroglycerin. Absorption via the oral mucosa is rapid and by-passes the liver, leading to increased bioavailability. Thus, rapid and efficient symptom relief by nitroglycerin may be achieved with sublingual or buccal tablets, or

an oral spray. Buccal tablets have a longer duration of action and may be useful for situational prophylaxis. Nitroglycerin tablets decay when exposed to air, and opened containers should be discarded within 3 months; spray formulations are stable.

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 MI. 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.<sup>157,377,495,496</sup> Long-acting nitrate treatment is only symptomatic, as studies after MI have failed to show prognostic benefit of such treatment.<sup>497,498</sup> Side effects are mainly related to vasodilatation, i.e. headaches and flushing, as described earlier.

Several long-acting nitrates are available. Isosobide dinitrate (ISDN) has an intermediate duration of action, and requires more than once daily dosing. Isosorbide-5-mononitrate (ISMN) is supplied in various formulations that provide extended action of a suitable duration (see below). Nitroglycerin patches for transdermal treatment allow full control of the duration of action, but are more expensive than ISDN or ISMN.

Nitrate tolerance may develop when nitrate levels are continuously maintained above a certain threshold level, and results in poorer protection against angina attacks and resistance to the pain relieving effects of short-acting nitroglycerin. Thus, 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; a decreased anginal threshold and rebound angina may, however, occur when patches are removed.<sup>499-501</sup> Transdermal nitroglycerin has been more clearly associated with rebound ischaemia than oral long-acting nitrate treatment.<sup>495</sup>

**Beta-blockers.** Beta-blockers are well documented for the prevention of anginal symptoms and ischaemia.<sup>157,377,502,503</sup> 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.<sup>425</sup> Beta-blockers are also well established in the treatment of hypertension.<sup>286</sup>

Beta-1 selective antagonists are as effective as non-selective antagonists,<sup>157</sup> indicating that the beta-1 selective sympathetic neurotransmitter, noradrenaline, is the primary beta-adrenergic target for inhibition. Beta-1 selective

agents are preferred due to advantages concerning side-effects and precautions compared with non-selective beta-blockers.<sup>157,377</sup> Commonly used beta-1 blockers with good documentation as anti-anginal drugs are metoprolol, atenolol, and bisoprolol. The anti-anginal and anti-ischaemic effects are related to the degree of cardiac beta-1 adrenoceptor blockade, i.e. to the plasma concentration of the drug, whereas the blood pressure lowering effect in hypertension is not. 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 od, metoprolol CR 200 mg od, atenolol 100 mg/day od (or 50 mg bid). The degree of beta-blockade may be assessed by exercise testing. Beta-blockers are effective anti-anginal drugs which increase exercise tolerance, and decrease symptoms and short-acting nitrate consumption.<sup>157,377,502,503</sup> 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.<sup>504</sup> Similarly, depression was not increased among beta-blocker treated patients, and sexual dysfunction was only found in 5/1000 patient-years of treatment (leading to discontinuation in 2/1000).<sup>505</sup> Quality of life, which has been extensively studied in the treatment of hypertension, is well preserved with beta-blocker treatment of hypertensive patients,<sup>505,506</sup> but this has not been systematically studied in patients with stable angina.<sup>379</sup> Psychosocial variables reflecting quality of life were similarly influenced by metoprolol and verapamil treatment in the APSIS study.<sup>49</sup> Thus, the side-effect profile of beta-blockade may not be as unpalatable to patients as commonly perceived.

**Calcium channel blockers.** CCBs are also well established anti-anginal agents.<sup>157,377,467,502,503</sup> 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 CCBs (verapamil and diltiazem) also to some degree reduce myocardial contractility, heart rate, and A-V nodal conduction.<sup>157,377</sup> Even vasoselective dihydropyridine CCBs (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.<sup>507</sup>

Long-acting CCBs (e.g. amlodipine) or sustained release formulations of short-acting CCBs (e.g. nifedipine, felodipine, verapamil, and diltiazem) are preferred, to minimize fluctuations of plasma concentrations and cardiovascular effects.<sup>508</sup> 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 CCBs. Verapamil may cause constipation.

The anti-anginal effects of CCBs are related to decreased cardiac work due to systemic vasodilatation, as well as coronary vasodilatation and counteraction of vasospasm.<sup>157,377</sup> CCBs are especially effective in patients with vasospastic (prinzmetal) angina, but in some patients CCBs may, however, increase ischaemia.<sup>509</sup>

The CAMELOT study<sup>467</sup> showed that the anti-anginal effects of amlodipine compared with placebo treatment significantly reduced hospitalization for angina, as well as the need for revascularization during a 2-year follow-up. Enalapril treatment was not associated with similar effects on ischaemia-related outcomes. In the CAPE study,<sup>510</sup> treatment with amlodipine compared with placebo resulted in a modest, but significant further reduction of ischaemia 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 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 MI, 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,  $P = 0.002$ ).<sup>493</sup>

The anti-anginal and anti-ischaemic effects of CCBs are additive to those of beta-blockers in many, but not all patients. Dihydropyridine CCBs are suitable for combination with beta-blockers, which counteract the reflexogenic cardiac sympathetic activation. Heart rate lowering CCBs may cause conduction disturbances in predisposed patients treated with beta-blockers. All CCBs may precipitate heart failure in predisposed patients. Attempts to use dihydropyridine CCBs for vasodilator treatment of heart failure have not been successful. However, amlodipine may be used for the treatment of angina in patients with compensated heart failure if not controlled by other therapy (i.e. nitrates, beta-blockers).<sup>511</sup>

**Comparison of beta-blocker and calcium antagonist (CCB) treatment in stable angina.** The IMAGE study<sup>512</sup> compared patients with stable angina treated with metoprolol CR 200 mg od or nifedipine SR 20 mg bid 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.<sup>513</sup> However, although exercise-induced ischaemia was predictive of cardiovascular events in the study,<sup>513</sup> short-term treatment effects on exercise-induced ischaemia did not independently predict improvement in long-term outcome. This highlights the important difference between treatment of symptoms and ischaemia and treatment aimed prognosis. Severity of ischaemia on baseline assessment acts as a marker of the underlying severity of coronary disease. But it is the severity of disease which influences the likelihood of plaque destabilization, and the propensity to and severity of thrombotic complications if and when plaque becomes unstable,

factors which are not modified by traditional anti-ischaemic agents.

The TIBBS study<sup>514</sup> 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 because of side-effects in the nifedipine group compared with the atenolol and the combination groups.<sup>48,515</sup> Meta-analyses comparing effects of beta-blockers and CCBs in stable angina pectoris indicate that beta-blockers are more effective than CCBs in reducing anginal episodes,<sup>494</sup> but that effects on exercise tolerance and ischaemia of the two drug classes are similar.<sup>157,494</sup>

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 CCBs.** There are relatively few studies comparing anti-anginal and anti-ischaemic effects of long-acting nitrates with beta-blockers or CCBs, and there is no documentation concerning possible effects of nitrates on morbidity in stable angina pectoris.<sup>494</sup> There were non-significant trend towards less nitroglycerin use with beta-blockers, and fewer angina episodes per week with CCBs compared with long-acting nitrates in the meta-analysis by Heidenreich *et al.*<sup>494</sup> Thus long-acting nitrates have no overall therapeutic advantages over beta-blockers or CCBs.

**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.<sup>516</sup> Nicorandil is administered at a usual dose of 20 mg bid for the prevention of angina. Tolerance to the anti-anginal effect may develop with chronic dosing,<sup>517</sup> but cross-tolerance with nitrates does not seem to be a problem.<sup>516</sup> In addition to its anti-anginal properties, nicorandil is thought to have cardioprotective properties.<sup>516,518</sup> The Impact Of Nicorandil in Angina (IONA) trial showed a significant reduction of major coronary events in stable angina patients treated with nicorandil compared with placebo as add-on to conventional therapy.<sup>254</sup> 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;<sup>254</sup> thus the value of the treatment effect has been argued.<sup>518</sup> Nicorandil is not available in all countries.

**Other agents.** Sinus node inhibitors, such as ivabradine, act by selectivity inhibiting the cardiac pacemaker current  $I_f$ , and have negative chronotropic effects both at rest and during exercise.  $I_f$  inhibition has proven anti-anginal efficacy<sup>461,519,520</sup> and ivabradine may be used as an alternative

agent in patients who do not tolerate beta-blockade. It has been licenced by the EMEA for this purpose.

Metabolically acting agents protect from ischaemia by increasing glucose metabolism relative to that of fatty acids. Trimetazidine and ranolazine are both considered as metabolic anti-anginal drugs. However, ranolazine has also more recently been shown to be an inhibitor of the late sodium current,<sup>521</sup> which is activated in case of ischaemia, leading to calcium overload of the ischaemic myocardium, decreased compliance, increased LV stiffness, and compression of the capillaries. The inhibition of the late sodium current by ranolazine reverses these effects, and prevents calcium overload, and the subsequent consequences thereof.<sup>522,523</sup>

Both trimetazidine<sup>524–526</sup> and ranolazine<sup>527,528</sup> 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 licenced 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.<sup>529</sup> 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.<sup>530,531</sup> 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.

An algorithm depicting the strategy for medical management of stable angina, if revascularization is not considered necessary after initial evaluation and risk stratification, includes treatments aimed at improving prognosis and symptoms and is shown in *Figure 7*. The following recommendations pertain to anti-anginal therapy and 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 CCB (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 CCB (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.<sup>532</sup> As nitrates are effective in about half of the patients,<sup>303,532</sup> it is reasonable to start treatment with long-acting nitrates. If symptoms persist, calcium antagonists<sup>533</sup> and  $\beta$ -blockers,<sup>534</sup> which are beneficial in Syndrome X patients, may be added. Although  $\alpha$ -adrenergic blockade increases vasodilator reserve in patients with Syndrome X,<sup>535</sup>  $\alpha$ -adrenergic blocking agents are clinically inefficient.<sup>536,537</sup> There are reports that other drugs such as nicorandil<sup>538</sup> and trimetazidine<sup>539</sup> might be helpful in some patients.

ACE-inhibitors<sup>540</sup> and statins<sup>541</sup> are helpful to reverse underlying endothelial dysfunction. Thus, these drugs should be actively considered for patients with Syndrome X as part of their risk factor management,<sup>542</sup> and there are some data to suggest that ACE-inhibitors and statins may also be beneficial in reducing exercise-induced ischaemia in this population.<sup>541,543,544</sup>

The challenge of achieving long-lasting therapeutic effects in patients with Syndrome X requires a multidisciplinary approach.<sup>545</sup> This might include analgesic intervention using imipramine<sup>546</sup> or aminophylline,<sup>547</sup> psychological intervention,<sup>545</sup> electrostimulation techniques,<sup>548</sup> and physical training.<sup>549</sup> Some studies of transdermal hormone replacement therapy<sup>550,551</sup> in post-menopausal 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,  $\beta$ -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 vasospastic angina.** Removal of precipitating factors such as cessation of smoking is essential.<sup>552</sup> The main elements of drug therapy are nitrates and calcium antagonists. Although nitrates are highly effective in abolishing acute vasospasm, they are not as successful in preventing attacks of resting angina.<sup>340</sup> CCBs 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/d verapamil, up to 260 mg/d diltiazem, up to 120 mg/d nifedipine). However, calcium antagonists achieve a complete resolution of symptoms in only 38% of patients.<sup>340</sup> In most patients, a combination therapy with long-acting nitrates and high doses of calcium antagonists will result in an improvement of symptoms. In patients with resistant symptoms, addition of a second calcium antagonist of another class may be successful. Medical treatment seems to be more effective in women and in patients with ST-elevation during provocation testing.<sup>340</sup>

The role of  $\alpha$ -blockers is controversial but occasional therapeutic benefit has been reported.<sup>553</sup> Nicorandil, a potassium channel activator, may also be useful in occasional patients with refractory vasospastic angina.<sup>554</sup> Reports of success in treating drug-resistant focal vasospasm by coronary artery stenting exist,<sup>555,556</sup> but this approach is not advocated for widespread application. CABG is not indicated because spasm distal to the anastomosis may occur.

Spontaneous remission of spasmodicity occurs in about half of western people following medical treatment for at least 1 year.<sup>557</sup> Thus, it is acceptable to taper and discontinue treatment 6–12 months after angina has disappeared 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, coronary artery bypass graft (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. 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. 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

Favorolo first described the use of saphenous vein to bypass a diseased coronary artery in 1969. Since then CABG has become the most common operation for CAD and one of the most commonly performed surgical operations worldwide. There are two main indications for CABG: prognostic and symptomatic. Prognostic benefit of CABG is mainly due to a reduction in cardiac mortality, as there is less evidence for reduction in MI.<sup>69,290</sup> Evidence of prognostic benefit of CABG compared with medical therapy has not been demonstrated in low-risk patients (annual mortality <1%).<sup>69</sup> 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 2.8%, which by contemporary standards appears high. Further observational data from the Duke registry confirmed that long-term mortality benefit associated with surgery was limited to high-risk groups.<sup>558</sup> Analyses of observational and randomized controlled trial data have revealed that the presence of specific coronary artery anatomy is associated with a better prognosis with surgery than with medical treatment.<sup>69,288</sup> Such disease includes the following:

- (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.<sup>287,559</sup>

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.<sup>290</sup> 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 and 4%<sup>51,560–563</sup> depending on the population studied, and there are well-developed risk stratification models available for the assessment of risk in individual patients.<sup>564,565</sup> There is the paradox that the higher the risk of operation, the greater is the benefit of surgical over medical treatment. Most patients are angina-free following CABG, but recurrent angina may occur in the years after surgery. Although the long-term patency rates for the left internal thoracic artery (LITA) graft are extremely good, saphenous vein grafts have a significant rate of attrition. Thrombotic occlusion can occur in the early post-operative period,  $\sim 10\%$  by the end of the first year, and after 5 years, the vein itself can develop atheromatous disease. The patency rate of vein grafts is 50–60% at 10 years.<sup>566,567</sup>

Over the last 20 years, the standard procedure has been to graft the LAD with the LITA and use saphenous vein for the other bypass grafts. Because at least 70% of patients are alive 10 years following surgery, 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 MI, recurrent angina, and the need for further cardiac interventions.<sup>568</sup> Recent observational studies have suggested benefit for bilateral internal thoracic artery (BITA) grafting.<sup>569</sup> There appears to be significant survival benefit when using BITA grafts irrespective of age, ventricular function, and the presence of diabetes. Furthermore, the benefit of using BITA increased with the duration of follow-up, particularly in terms of the need for redo surgery, which at 10 years was 40% for single ITA and 8% for BITA grafting in well-matched patients. Ten years after CABG 90% of ITA grafts continue to function well. With experience, including the use of skeletonized ITA pedicles, the risk of sternal devascularization and subsequent dehiscence is much reduced, even in diabetics. 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  $> 90\%$  in the first 3 years of surgery.<sup>570,571</sup>

The use of extra-corporeal circulation (cardiopulmonary bypass) to perform coronary artery surgery remains the most commonly used approach. But there are risks attached, including a whole-body inflammatory response and the production of micro-emboli. The need for aortic cannulation and manipulation of the ascending aorta may lead to release of emboli, especially in elderly, atheromatous patients. The so-called 'off-pump' surgery may lead to a reduction in peri-operative mortality and morbidity. The recent introduction of stabilization devices, which allow isolation and control of epicardial arteries, facilitates attachment of the bypass graft without stopping the heart and has enabled surgeons to perform surgery without the use of cardiopulmonary bypass. Randomized trials comparing off-pump with the standard procedure are now available. Although the use of blood products was reduced in the

off-pump group (3 vs. 13%) and the release of CK-MB isoenzyme was 41% less in the off-pump group, there were no differences in the peri-operative complication rates. There was no difference in outcome in the first 1–3 years after surgery between off-pump and standard groups.<sup>572,573</sup> More recently, Khan *et al.*,<sup>574</sup> in a further randomized trial with angiographic follow-up of 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 one-vessel disease, advances in experience, equipment, particularly stents, and adjuvant therapy, have led 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 one- or multi-vessel PCI with a high likelihood of initial procedural success and acceptable risk.<sup>575</sup> The risk of death associated with the procedure in routine angioplasty is ~0.3–1%, although this can vary quite considerably. Contrary to the case of bypass surgery, on available evidence, PCI compared with medical therapy does not seem to provide substantial survival benefit in stable angina.<sup>576</sup>

Trial-based evidence indicates, however, that PCI is more often effective than medical treatment in reducing events that impair quality of life (angina pectoris, dyspnoea, and the need for re-hospitalisation or limitation of exercise capacity). The ACME investigators<sup>577</sup> 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 two-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 one-vessel disease.<sup>578</sup> This small study ( $n = 328$ ) suggests that PCI may be less effective in controlling symptoms in patients with two-vessel and stable angina when compared with one-vessel disease.

The RITA-2 trial<sup>579</sup> showed that PCI results in 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 peri-procedural MI. In this trial, 1018 patients (62% with multi-vessel 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. Death and definite MI occurred in 6.3% of the PCI patients and 3.3% of the medical patients ( $P = 0.02$ ). Of the 18 deaths (11 PCI and seven medical), only eight were due to heart disease. Twenty-three per cent of the medical patients required a revascularization procedure during follow-up. Angina improved in both groups, but there was a 16.5%

absolute excess of worse angina in the medical group at 3 months following randomization ( $P < 0.001$ ). During follow-up, 7.9% of the patients randomized to PCI required CABG surgery when compared with 5.8% of the medical patients. AVERT<sup>580</sup> 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 drug-eluting stents (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 MI or the need for CABG surgery. However, coronary stenting reduces the rate of restenosis and the need for repeat PCI,<sup>581</sup> findings confirmed in a further more recent meta-analysis.<sup>582</sup> 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%.

Drug-eluting stents have been the focus of attention of interventional coronary therapy after the RAVEL study.<sup>583</sup> The frequently interchangeable use of the term 'coated stent' and 'drug-eluting stent' is misleading because coated stent also includes the so-called passive coatings, which have failed to prove their benefit and, in some series, have even showed harmful effect. Hence, the term drug-eluting stent is recommended instead of coated stent. 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 one-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 over 9 months range between 7.1 and 10.3% with drug-eluting stents compared with between 13.3 and 18.9%.<sup>584–586</sup> More specific guidelines on the use of DES are available in the ESC guidelines on PCI.<sup>587</sup>

### 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<sup>70</sup> 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)<sup>588</sup> 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 due to 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)<sup>589</sup> 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, and 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,<sup>562,597,598</sup> and in multi-vessel as well as one-vessel disease. Meta-analysis of trials conducted before 1995,<sup>599</sup> when coronary stenting was rare, revealed no significant differences in the treatment strategies for either death and the combined endpoint of death and 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.<sup>590</sup>

More recent trials, such as the ARTS<sup>600</sup> and SOS trials,<sup>597</sup> have incorporated the use of stents as part of PCI. The ARTS 1 trial<sup>600</sup> compared the strategy of multiple-stent implantation with the aim of complete revascularization vs. bypass surgery in patients with multi-vessel disease. 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, and 6 and 5%, respectively, had silent ischaemia. As in previous analyses of balloon angioplasty, at 1 year, there was no difference between the two groups in terms of rate of death, stroke, or MI. Among patients who survived without stroke or MI, 16.8% of those in the stenting group underwent a second revascularization, when compared with 3.5% of those in the surgery group. The rate of event-free survival at 1 year was 73.8 percent among the patients who received stents and 87.8 percent among those who underwent bypass surgery. As measured 1 year after the procedure, coronary stenting for multi-vessel disease in selected patients offered a similar outcome in terms of death, stroke, and MI as bypass surgery. However, stenting was associated with a greater need for repeated revascularization.

A meta-analysis including trials of stents<sup>560</sup> suggests a mortality benefit with CABG compared with PCI at 5 years which continued to 8 years in patients with multi-vessel disease, 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 percutaneous intervention 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.<sup>601</sup> 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.<sup>602</sup>

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 1–2-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).<sup>70</sup>



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 in whom surgical risk is prohibitively high may benefit from revascularization by PCI, particularly when residual viability can be demonstrated in the dysfunctional myocardium perfused by the target vessel(s). This issue is currently addressed in two large randomized studies, the STICH<sup>603</sup> and the HEART UK<sup>604</sup> trials.

**Unprotected LM disease.** The LM stem is referred to as unprotected when the distal coronary arteries do not receive circulation from a bypass graft. Several observational reports<sup>605,606</sup> indicate the feasibility of PCI in LM stem disease. More recently, an observational registry has shown improved results with drug eluting compared with bare metal stents<sup>607</sup> holding promise for the use of PCI in LM stem disease in the future. However, surgery should remain the preferred approach until the outcome of further trials are known.

**Multi-vessel disease in patients with diabetes.** A formal trial comparing the effect of PCI vs. CABG in diabetics is not yet available; however, *post hoc* subgroup analyses of randomized trials comparing these treatment strategies have shown reduced mortality with bypass surgery compared with PCI.<sup>608,609</sup> The BARI trial was the largest of these trials and the only in which a statistical difference in mortality was detected between the treatment groups in the diabetics.<sup>590,610</sup> Among treated diabetics ( $n = 353$ ), there was an absolute survival advantage of 15% for CABG at 5 years ( $P = 0.003$ ). The rate of repeat revascularization was also higher with PCI in diabetics in BARI and was evident too even with stent-assisted PCI (41 vs. 8.4%) in the ARTS study.

A limitation of these trials is that they were conducted before the widespread use of drug-eluting stents or adjuvant peri-procedural antiplatelet therapy. Drug-eluting stents have reduced the rate of restenosis in diabetic as in non-diabetic patients<sup>585,586,611</sup> but the impact of this reduction on mortality in diabetic patients, particularly in multi-vessel PCI, is unknown. Two major trials are underway to address this important issue, BARI 2 Diabetes (BARI 2D) and FREEDOM (Future Revascularisation 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 multi-vessel disease until the results of further trials are known.

**Patients with previous bypass graft surgery.** There are no randomized controlled trials comparing treatment options in patients with previous bypass surgery. Observational data suggest that patients with late stenoses of vein grafts have a high mortality rate,<sup>612</sup> and re-operation improved the outcome of these patients in one observational comparison.<sup>613</sup> Redo surgery may be undertaken on symptomatic grounds where the anatomy is suitable. However, the operative risk of redo bypass surgery is as high as three-fold greater than initial surgery,<sup>614</sup> and for those with a patent ITA graft, there is the additional risk of damage to this graft during surgery.

In contrast, 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. Protective filter devices may be employed to reduce particulate debris from embolizing downstream and causing peri-procedural myocardial damage (SAFER)<sup>615</sup> when dilating old saphenous vein grafts.

**Chronic total occlusions.** Chronic total occlusions still represent the most frequent mode of failure of PCI. When the occlusion can be crossed with a guide-wire and the distal lumen has been reached, satisfactory results are obtainable with stent implantation, as shown by several trials,<sup>616-618</sup> albeit at the expense of high restenosis rate ranging from 32 to 55%. The value of drug-eluting stents in this respect is currently under evaluation. In patients with multi-vessel disease, 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 8* 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 symptomatology. 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 peri-procedural morbidity and mortality
- (2) likelihood of success, including factors such as technical suitability of lesions for angioplasty or surgical bypass
- (3) risk of restenosis or graft occlusion

**Table 8** Summary of recommendations for revascularization in stable angina

Indication	For prognosis <sup>a</sup>		For symptoms <sup>b</sup>		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–IV despite medical therapy with one-vessel disease			I	A	ACME and MASS
Angina CCS classes I–IV despite medical therapy with multi-vessel disease (non-diabetic)			I	A	RITA 2 and 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, and Yusuf 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–IV with multi-vessel disease (diabetic)	IIa	B	I	B	BARI, GABI, ERACI-I, SoS, ARTs, Yusuf <i>et al.</i> , Hoffman <i>et al.</i>
Angina CCS classes I–IV with multi-vessel disease (non-diabetic)			I	A	
Angina CCS classes I–IV despite medical therapy and one-vessel disease including severe disease of the proximal LAD			I	B	MASS
Angina CCS classes I–IV despite medical therapy and one-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 symptomatology.

CCS, Canadian Cardiovascular Society.

<sup>a</sup>Relates to effects on mortality, cardiac or cardiovascular mortality, or mortality combined with MI.

<sup>b</sup>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.

- (4) completeness of revascularization. If considering PCI for multi-vessel disease, 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 the following.

- (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 one- 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 one- 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 multi-vessel disease 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 one-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 multi-vessel disease without high-risk coronary anatomy, 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)

##### **Class IIa**

- (1) PCI for one-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 one-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 for multi-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 does not outweigh potential benefit (level of evidence A)
- (4) PCI for multi-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)

##### **Class IIb**

- (1) CABG for one-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 the estimated annual mortality (level of evidence B)

#### **Treatment of stable angina: multi-targeted treatment of a multi-faceted disease**

In his/her lifetime, the patient with stable angina may meet episodes of exercise/stress-induced symptomatic myocardial ischaemia (angina pectoris), silent ischaemia, progressive angina, acute coronary syndromes (unstable angina and MI), acute and chronic heart failure, and life-threatening arrhythmias. Prolonged periods of stability may alternate with periods of instability (sudden progression and acute coronary syndromes). According to the state of the disease, a patient will require treatment aimed at retardation of the progression of disease (prevention), management of symptomatic disease (angina pectoris), management of acute coronary syndromes, and management of heart failure or life-threatening arrhythmias. The physician should be prepared to offer the appropriate therapy at the appropriate time. The different modes of preventive therapy, symptomatic medical therapy, such as percutaneous and surgical coronary revascularization and management of arrhythmias, are all rapidly evolving and so it is recommended that an individual physician operates within a team which can offer the appropriate therapy at the appropriate time with the appropriate skills.

#### **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<sup>619</sup> and also the preponderance of male-specific data in the published literature.

There are numerous differences in the epidemiology and primary manifestation of 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.<sup>40,41,620</sup> Although the incidence of

CHD death and MI is greater in men than in women at all ages, the incidence of angina in women exceeds that of men in post-menopausal age groups. Therefore, it is not surprising that at population level, some studies report an even higher prevalence of Rose angina questionnaire in middle aged and elderly women than in men of comparable age.<sup>31–33,621,622</sup> However, in population-based studies, the incidence of fatal CHD is higher in men with angina than women with angina,<sup>620</sup> 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.<sup>623</sup>

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,<sup>624</sup> 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 and non-cardiac chest pain.

Angina, the symptom complex, may still be associated with ischaemia even in the absence of obstructive coronary lesions, as in Syndrome X, a phenomenon which is more common in women. Microvascular disease and coronary vasospasm are also more common in women. Ischaemia, in this context, may be demonstrated electrocardiographically, by perfusion scintigraphy, or other methods and may respond appropriately to anti-ischaemic therapy without angiographic evidence of epicardial stenosis. Although the absence of obstructive coronary lesions remains an indicator of better infarct-free survival than the presence of obstructive disease, there are some emerging data suggesting that the prognosis associated with 'normal' coronary arteries is not as benign as once thought.<sup>305</sup>

When used for the detection of significant coronary disease, exercise ECG testing has a higher false-positive rate in women (38–67%) than in men (7–44%),<sup>140</sup> largely because of the lower pretest likelihood of disease,<sup>142</sup> but a lower false-negative rate in women.<sup>625</sup> 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 radionuclide perfusion scans may be lower in women than men.<sup>626</sup> Artefacts due to breast attenuation, usually manifest in the anterior wall, can be an important caveat in the interpretation of women's perfusion scans, especially when <sup>201</sup>Tl is used as a tracer. More recently, the use of gated <sup>99m</sup>Tc sestamibi SPECT imaging has been associated with an apparent reduction in breast artefacts.<sup>627</sup> Similarly, exercise or pharmacological stress echocardiography may help avoid artefacts 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.<sup>171,628,629</sup>

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 to be referred for further testing.<sup>630</sup> 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.<sup>630</sup>

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 MI than men, and it has been suggested by some that less vigorous treatment in women may impact on reduced survival in women after MI.<sup>631</sup> A review of 27 studies concluded that the reasons for increased early mortality among women were older age and the presence of other unfavourable baseline clinical characteristics.<sup>632</sup> 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.<sup>633</sup>

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 and 368 women) with angiographically documented CAD were evaluated over a 16-year period (1981–97). Over time, the number of angioplasty procedures increased significantly from 11.6–23.2% for men and from 17.6–28.0% for women, whereas the number of coronary artery bypass procedures decreased in men from 34.9% to 29.5% and from 42.6–30.6% in women.<sup>634</sup> However, interpretation of this and other coronary arteriography registries is limited by their intrinsic referral bias. Data from the Euro Heart Survey of Stable Angina conducted in 2003 suggest that 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.<sup>635</sup> 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, 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.<sup>81,636-638</sup> Moreover, a number of epidemiological reports indicate that in patients with diabetes, the higher the blood glucose, the greater the incidence of CVD.<sup>639,640</sup>

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.<sup>641</sup>

There is growing interest in the use of myocardial perfusion scanning and other techniques to detect ischaemia in asymptomatic diabetic individuals<sup>642</sup> and firm evidence of the prognostic power of perfusion imaging specifically in diabetic patients.<sup>643</sup> There are also data to suggest that individuals with diabetes may have subclinical ventricular dysfunction which negatively impacts on exercise capacity,<sup>644</sup> 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 testing, and coronary arteriography. As CVD accounts for 80% of mortality in patients with diabetes mellitus,<sup>645</sup> 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 physiological control of blood glucose and control of other risk factors such as dyslipidaemia, renal disease, obesity, and smoking. Abundant evidence 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 type 2 is now available.<sup>645-648</sup>

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. Additionally, ACE-inhibitors are indicated in diabetic patients with proven vascular disease.<sup>253</sup> 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 multi-vessel disease and of restenosis.<sup>649,650</sup> Thus, even after successful invasive procedures, good management of CVD risk factors and a tight glycaemic control are essential for good long-term outcome.<sup>638</sup>

### Elderly

After the age of 75 years there is an equal prevalence of CAD in men and women.<sup>651</sup> The disease is more likely to be diffuse and severe; LM coronary artery stenosis and three-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.<sup>652</sup> In large community studies of men and women >65-years old, those with atypical symptoms and typical angina were shown to have similar 3 year cardiac mortality rates.<sup>20</sup> 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 occur more frequently with increasing age, especially at higher workloads.<sup>653</sup> The interpretation of exercise test results in the elderly differs from that in the young. The higher prevalence of disease means that more test results are false negative.<sup>654</sup> False-positive test results also are more frequent because of the higher prevalence of confounders such as prior MI, LV hypertrophy from valvular diseases, hypertension and conduction disturbances. Despite these differences, exercise testing remains important also in the elderly. The Task Force believes that exercise ECG testing should remain the initial test in evaluating elderly patients with suspected of 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.<sup>243</sup> However, age >75 is an important predictor of contrast-induced nephropathy.<sup>655</sup>

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.<sup>656</sup> 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,<sup>438</sup> 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.<sup>657-659</sup>

### 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. It is an unfortunate irony that the prolongation of life due to the improvement of cardiovascular care and treatment are responsible for an increase in the number of patients with end-stage ischaemic coronary disease, some who complain from intractable episodes of angina. 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.<sup>660</sup>

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.

According to the previously mentioned report from the Joint Study Group, we have no accurate figures on the occurrence and frequency of refractory angina. A Swedish survey of patients referred for coronary arteriography because of stable angina pectoris performed in 1994–95 showed that nearly 10% of patients were rejected for revascularization despite severe symptoms.<sup>661,662</sup>

The most common reasons that revascularization is not considered appropriate are:

- (1) Unsuitable anatomy
- (2) One or several previous bypass grafting and/or PTCA procedures
- (3) Lack of available graft conduits
- (4) Extra-cardiac diseases which increase perioperative morbidity and mortality
- (5) Advanced age, often in combination with these factors

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, although not all have been successful: neuromodulation techniques (transcutaneous electric nerve stimulation and spinal cord stimulation), thoracic epidural anaesthesia, endoscopic thoracic sympathectomy, stellate ganglion blockade, transmyocardial or percutaneous laser revascularization, angiogenesis, enhanced external counterpulsation, heart transplantation, and 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.<sup>663–665</sup> 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.

Enhanced external counterpulsation (EECP) is an interesting non-pharmacological technique, which has also been investigated largely in the USA. Two multi-centre registries have evaluated the safety and effectiveness of EECP.<sup>666–668</sup> The technique is very well tolerated when used over a period of 35 hours of active counterpulsation during 4–7-week period. Anginal symptoms were improved in ~75–80% of patients.

Transmyocardial 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 revascularization 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.<sup>669</sup> Mortality did not differ significantly between the two groups. Other studies of transmyocardial revascularization (either surgically or percutaneously) have been unable to confirm this benefit.<sup>670,671</sup> In particular, a recent randomized controlled trial of 298 patients showed that treatment with percutaneous myocardial laser provides no benefit beyond that of a similar sham procedure in patients blinded to their treatment.<sup>672</sup> Furthermore, measurement of regional myocardial blood flow and coronary flow reserve by means of PET has failed to show improved perfusion following this procedure.<sup>673</sup>

International studies and registries are urgently required to clarify the epidemiology of this condition and further research is encouraged to definitely establish the roles of existing and novel alternative techniques to manage these patients.

## 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 ECG.
- (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 of 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 is not possible or the ECG is not interpretable, or in addition to exercise testing when the diagnosis remains uncertain or functional assessment is inadequate.
- (5) In addition to their role in initial 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, 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 purposes 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 symptomatic 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 strongly 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 advisable 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<sup>674,675</sup> 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 worrying 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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