 Guidelines

Management of stable angina pectoris

Recommendations of the Task Force of the European Society of Cardiology

Introduction

Stable angina pectoris is a common and disabling disorder. In recent years, its pathophysiology has been clarified and there have been major advances in its diagnosis and management. There is, however, no consensus as to the optimal strategy of investigation and treatment. Furthermore, its therapy has not been subjected to the same scrutiny by large randomized trials as has, for example, that of myocardial infarction and unstable angina. Thus, although much has been achieved in comparing the symptomatic benefit of different modalities of treatment, there is a relative paucity of information about their prognostic effects.

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 availability of resources and the cost.

Definition and pathophysiology

Heberden[1] introduced the term ‘angina pectoris’ in 1772 to characterize a syndrome in which there was ‘a sense of strangling and anxiety’ in the chest, especially associated with exercise. He did not recognize its cardiac origin but, within a few years, others[2] had demonstrated coronary artery disease at the necropsy of patients who had experienced the symptoms. It is now usual to confine the term to cases in whom the syndrome can be attributed to myocardial ischaemia, although essentially similar symptoms can be caused by disorders of the oesophagus, lungs or chest wall. In this Task Force report, the term is used for chest discomfort due to myocardial ischaemia associated with coronary artery disease, although it is recognized that there are other important causes of angina, such as aortic stenosis and hypertrophic cardiomyopathy that must not be overlooked.

Anginal symptoms are regarded as stable if they have been occurring over several weeks without major deterioration. They typically occur in conditions associated with increased myocardial oxygen consumption. Even in stable angina, however, symptoms may vary considerably from time to time, depending upon such factors as ambient temperature and emotional stress.

Angina is said to be unstable if pre-existing angina worsens abruptly for no apparent reason or when new angina develops at a relatively low work load or at rest. This form of angina is often associated with fissuring or rupture of an atherosclerotic plaque and subsequent intracoronary thrombus formation. Increases in coronary artery tone or spasm are important factors in some cases.

Many patients presenting with anginal symptoms do not fulfill the above definitions. For example, new symptoms may have developed in recent weeks but have not progressed. Pathologically, they may have features of both stable and unstable angina, and the prognosis is intermediate between these two better defined syndromes.

Angina is variant or of the Prinzmetal type if it develops spontaneously with ST elevation on the electrocardiogram. This is usually ascribed to an increase in coronary tone or spasm, and may then be termed vasospastic.

The term Syndrome X is applied to a syndrome in which angina pectoris is accompanied by objective evidence of myocardial ischaemia (such as ST depression on the electrocardiogram) in the absence of apparent coronary atherosclerosis or other organic disease of the epicardial coronary arteries. ‘Small vessel disease’ may, however, be present.

Angina pectoris occurs when there is an imbalance between myocardial perfusion and the demands of the myocardium. The pathological substrate for this is almost invariably atheromatous narrowing of the coronary arteries. It is usually considered that a coronary artery must be narrowed by at least 50–70% in luminal diameter before coronary blood flow is inadequate to meet the metabolic demands of the heart with exercise or stress. However, the importance of a stenosis depends not only on the reduction in luminal diameter but, also on the length and number of stenoses. In addition, the luminal diameter of stenoses, particularly eccentric stenoses, are not fixed and may alter with changes in coronary tone due to local smooth muscle constriction or dilatation. This may occur as a response to the release

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Request for reprints to: European Heart Journal, W. B. Saunders, 24–28 Oval Road, London NW1 7DX, U.K.
of various hormones and neurogenic stimuli. Very occasionally, spasm of the coronary arteries can occur in the presence of apparently normal coronary arteries, but even in these circumstances minor plaques or damage to the endothelium are frequently present.

Although the initiating stimulus causing an episode of angina may be an increase in myocardial oxygen demand or decrease in coronary blood flow due to vasoconstriction at the site of an atheromatous narrowing, the subsequent sequence of events invariably lead to segmental dysfunction and/or left ventricular dilatation causing a fall in coronary blood flow. Also the shortened diastolic filling time due to the tachycardia that develops and various hormonal perturbations may lead to coronary vasoconstriction. At the same time, the increases in heart rate and blood pressure that usually follow the development of myocardial ischaemia lead to a further increase in myocardial oxygen demand. Finally, not only may coronary tone alter but the heart can also adapt its metabolic demands. Chronic or recurrent episodes of ischaemia may lead to an adaptive process in myocardial metabolism that can result in ‘hibernating’ myocardium, defined as chronic but reversible ischaemic left ventricular dysfunction.

Patients with coronary artery disease are at risk of developing plaque fissuring or rupture. Once plaque rupture occurs, this is usually followed by platelet aggregation at the same site, which may lead to (further) impairment of coronary blood flow or even thrombotic coronary occlusion. Furthermore, activated platelets at the site of plaque rupture may release a series of vascular active substances which will lead to increased vasomotor tone or even spasm. The clinical syndrome associated with these events may be labelled either unstable angina or evolving myocardial infarction.

**Epidemiology**

The diagnosis of angina pectoris has, until relatively recently, depended largely upon obtaining a characteristic history. Reliable estimates of incidence and prevalence based upon such evidence have been difficult to obtain. The cardiovascular questionnaire developed by Rose and Blackburn has been widely used in studies on the prevalence of angina pectoris in populations. A positive response to this questionnaire, however, overestimates the prevalence of angina pectoris in comparison with a history taken by a physician, with particularly high proportions of false positives in younger women, as shown in a population-based study carried out in Finland. Similar or even higher proportions of false positives have been reported from other studies. Population-based studies using various data collection methods in countries with high or relatively high coronary heart disease rates have shown that among middle-aged people angina is more than twice as common in men as it is in women. In both sexes the prevalence of angina increases sharply with age: in men from 2–5% in the age group 45–54 years to 11–20% in the age group 65–74 years, and in women from 0.5–1% to 10–14%, respectively. After the age of 75 years the prevalence is almost similar in men and women. On the basis of these studies it may be estimated that in countries with high or relatively high coronary heart disease rates the total prevalent number of persons with angina may be as high as 30,000–40,000 per 1 million total population. In more than one half of patients with angina the severity of symptoms seriously limits their everyday activities, often leading to premature retirement in patients of working age.

Population-based information on the incidence of angina pectoris is mainly based on prospective epidemiological studies with repeated re-examinations of study cohorts. During a 10-year follow-up of the Seven Countries Studies cohorts, the average annual incidence of angina pectoris as the only manifestation of coronary heart disease was in men aged 40–59 years 0.1% in Japan, Greece and Croatia, 0.2–0.4% in Italy, Serbia, Netherlands and U.S.A., and 0.6–1.1% in Finland. These incidence rates showed a significant positive correlation with coronary heart disease mortality rates in the study cohorts. In the 20-year follow-up of the Framingham Study cohort, the annual incidence of uncomplicated angina pectoris among men was 0.3% in the age group 45–54 years, 0.8% in the age group 55–64 years and 0.6% in the age group 65–74 years. Among women the corresponding age-specific incidence rates were 0.2%, 0.6% and 0.6%. Angina pectoris was the presenting manifestation less frequently in men than in women (37% vs 65%), but due to generally higher incidence rate of clinically manifest coronary heart disease in men there was a gap in the incidence of angina between the sexes below the age of 65 years.

Half of those having their first myocardial infarction had angina following it, whereas only one fifth of those having their first infarction had preceding angina. In the 5-year follow-up of the Israel Ischaemic Heart Disease Study cohort of men over 40 years of age, the average annual incidence of uncomplicated angina pectoris was 0.7%. A study based on the experience of a general practitioner in London over 25 years produced annual incidence rates close to those observed in the Framingham and Israel studies. This was 0.5% in persons above the age of 40 years, was higher in men than in women and increased with age; the gap between men and women diminished with advancing age.

Coronary heart disease mortality has been declining in a many industrialized, socio-economically well established countries in Europe and elsewhere. This decline has been most marked in younger middle-aged groups and it appears to be, in part, explained by a real decline in the incidence of the disease and in part by an improvement in the prognosis of those who get it. These favourable trends are, however, accompanied with a shift of the main burden of clinically manifest coronary heart disease, particularly its milder manifestations, towards older age groups, and in countries showing such trends the prevalence of angina pectoris can be predicted to increase in the older age groups. This has
recently been documented by morbidity statistics for England and Wales collected by the Royal College of General Practitioners in 1981–1982 and 1991–1992[10]. During the 10-year period the prevalence of angina pectoris increased in the age group 65–74 years by 63% in men and by 69% in women and in the age group 75 years and over by 79% in men and 92% in women.

Natural history and prognosis

Chronic stable angina is compatible with a relatively good prognosis in the majority of patients. Several studies have shown that mortality on average is approximately 2–3% per annum and a further 2–3% each year will sustain a non-fatal myocardial infarction[18–20]. There are, however, subgroups at higher risk: patients with significant impairment of left ventricular function, especially if heart failure has occurred. Another small subgroup with a poor outlook are those with malignant coronary anatomy: patients with left main stem stenosis or very proximal left anterior descending stenoses[21]. It is important as part of management to identify patients at high risk so that appropriate therapy is targeted to improve prognosis.

Nowadays, the ‘natural’ history of stable angina is affected by the complex and dynamic results of anti-ischaemic, anti-thrombotic, anti-hypertensive and lipid lowering therapy, as well as by revascularization procedures which lead to a new ‘managed’ history. Intensive risk factor modification may radically change the outcome of the disease. Reduction of lipid levels by diet, statins and other drugs, or ileal bypass have been shown to reduce coronary events and the need for revascularization. In stable angina pectoris patients, coronary atherosclerotic disease can progress subclinically, but usually does so slowly. Angiographically complex and smooth stenoses progress at different rates within the same coronary tree, the former changing more rapidly than the latter. Long-term progression of disease may be slow and linear or episodic and rapid, or a combination of both[22]. In patients with stable angina who had been advised to undergo coronary angioplasty in whom the coronary angiogram was repeated 73 months apart, a similar proportion of target and non-target lesions progressed rapidly (9% and 8% respectively), both contributing to the appearance of new symptoms[23]. These observations indicate that in patients with stable angina, coronary stenoses exist that may progress rapidly and that plaque events, rather than slow linear progression, can take place at the site of stenosis. These findings also indicate that progression of disease leading to clinical symptoms or outcome may not necessarily be related to the severity of the stenosis.

In many patients, smaller plaques are present in addition to those causing severe stenosis. The likelihood of instability or rupture of one of the many smaller plaques exceeds the risk of instability of the few areas with a marked stenosis[24]. The most severe stenosis in a vessel is not necessarily the one most likely to lead to infarction.

In the evaluation of patients with chronic stable angina it is important to identify those patients at increased risk whose outcome may be improved by revascularization. Information on long-term prognosis of patients with stable angina can be derived from the follow-up results of the large control groups of randomized trials aimed at evaluating the effectiveness of revascularization[25–27]. In general, the outcome is worse (and the revascularization–related improvement greater) in patients with worse left ventricular function, a greater number of diseased vessels, more proximal locations of coronary stenosis, greater severity of lesions, more severe angina, more easily provoked angina or ischaemia, and greater age.

Ischaemic episodes in patients with angina pectoris are often silent. Ambulatory silent ischaemia has been reported to predict adverse coronary events in some studies but not in others[28,29] and there is conflicting evidence that the suppression of silent ischaemia in stable angina pectoris improves cardiac outcome[30]. The significance and treatment of silent ischaemia in this context appears to be different from that of unstable and post-infarction angina where it has been clearly shown that recurrent ischaemia predicts an adverse outcome[31].

Diagnosis and assessment

Symptoms and signs

A carefully taken history is essential in the diagnosis and management 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 determine its cause and assess its severity.

The classic symptom has four cardinal features: location; relationship to exercise; character, and duration. Most patients can describe the first two characteristics without difficulty, but are less precise about the latter two.

Location. Typically the discomfort is located in the retrosternal region, and may radiate to both sides of the chest and the arms (more commonly the left) as far as the wrist, and to the neck and jaw. Less often, it may radiate to the back. Quite frequently, the pain starts in one of the other areas and only later spreads to the central chest; sometimes it does not involve the sternum at all.

Relationship to exercise. In most cases, angina is provoked by increased myocardial oxygen consumption during exercise (or other stress) and is quickly relieved by rest. Some patients experience angina at rest; this suggests either changes in coronary artery tone, arrhythmias, or unstable angina. However, emotion, a potent provoking factor, may be responsible.

Character. Although angina is often described as a pain, patients may deny this but acknowledge a discomfort.
which may be a feeling of pressure or a strangling sensation. The intensity of the symptoms varies greatly, from a slight localised discomfort to the most severe pain.

**Duration.** Anginal pain provoked by physical exercise is usually spontaneously relieved within 1–3 min after discontinuation of exercise, but may last up to 10 min or even longer after very strenuous exercise. Anginal pain provoked by emotion may be relieved more slowly than that provoked by physical exercise. Anginal episodes in patients with syndrome X are frequently longer and less consistent in their relation to exercise than those in patients with atherosclerotic coronary artery stenosis.

The chest discomfort may be accompanied by or even overshadowed by such symptoms as breathlessness, fatigue and faintness.

**Classification of angina**

The Canadian Cardiovascular Society[32] has provided a grading classification of angina:

- **Class I** ‘Ordinary physical activity does not cause angina’ — such as walking or climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation.
- **Class II** ‘Slight limitation of ordinary activity’ — walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold, or in wind, or when under emotional stress, or only during the few hours after awakening. Walking more than two blocks* on the level and climbing more than one flight of stairs at a normal pace and in normal conditions.
- **Class III** ‘Marked limitation of ordinary physical activity’ — walking one or two blocks on the level and climbing one flight of stairs in normal conditions and at normal pace.
- **Class IV** ‘Inability to carry on any physical activity without discomfort’ — anginal syndrome may be present at rest.

The Canadian classification has proved popular and is widely used, but alternative, and prognostically superior, instruments are available such as the ‘Specific Activity Scale’ and the ‘Duke Activity Status Index’.[33-35]

In clinical practice it is important to describe accurately the factors associated with angina pectoris in each individual patient. This should include specific activities associated with angina, walking distance, frequency and duration of episodes.

**Differential diagnosis of the symptoms.** If all four cardinal features are present, or even only the first two if they are quite typical, the diagnosis of chronic stable angina is virtually assured. Often, however, the picture is not so clear-cut and other diagnoses must be considered. Chief amongst these are oesophageal reflux and spasm, peptic ulcer, gallstones, musculo-skeletal disorders and non-specific chest pains, often associated with anxiety states.

**Physical signs.** There are no physical signs which are specific for angina, but those characteristic of an underlying cause (such as aortic stenosis) may be present. The patient often looks pale, distressed and sweaty during an attack. Third or fourth heart sounds may be heard as well as a murmur of (temporary) mitral incompetence.

**Evaluation for concomitant disorders.** Co-existent metabolic and clinical disorders are common. A full lipid profile should be obtained, and the appropriate clinical and laboratory examinations should be undertaken with respect to anaemia, hypertension, diabetes and thyroid function.

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*Equivalent to 100–200 m.*

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**ALGORITHM FOR THE DIAGNOSIS OF ANGINA PECTORIS, THE CHOICE OF INVESTIGATIONS**

While history often suffices to establish the diagnosis of angina pectoris, additional investigations are usually needed to confirm the diagnosis, to assess prognosis and to select the most appropriate therapy. Different strategies may be followed depending on the patient’s previous history and the severity (frequency and intensity) of their symptoms. In patients with new symptoms, in whom the diagnosis of coronary artery disease has not yet been established, the approach will differ in comparison with patients with known coronary artery disease, after previous coronary angiography or coronary intervention or after previous myocardial infarction.

Three diagnostic strategies can be distinguished:

1. It may be adequate to rely solely on the patient’s history, supplemented by physical examination and a resting electrocardiogram. This approach often suffices in elderly patients with mild symptoms responding promptly to medical therapy and in patients in whom coronary interventions are not considered a therapeutic option.

2. Another approach is based on a functional assessment of the presence or absence and extent of myocardial ischaemia, which may include exercise testing with electrocardiography, exercise (or other stress) myocardial perfusion imaging (thallium or one of the technetium-99m labelled perfusion tracers), stress-echocardiography and, possibly, exercise radionuclide angiography. In patients with significant functional abnormalities, this may be followed by coronary angiography to assess whether coronary intervention is indicated and which intervention would be most appropriate. The indications for coronary angiography are discussed in more detail below.
A further option is to proceed immediately from history, physical examination and ECG to coronary angiography. This approach may be indicated particularly in patients with typical and severe symptoms, including unstable angina, patients with early post infarction angina, and in patients with early recurrence of symptoms after previous coronary intervention\[36\].

In clinical practice, the second approach is followed most frequently. In patients with frequent or severe stable angina, functional assessment is often useful prior to or in addition to angiography. It should be appreciated that symptoms resembling angina do not necessarily have a causal relation to any coronary artery narrowings present. Thus, additional functional assessment may be needed in patients with less typical symptoms and moderately severe coronary artery narrowings. Furthermore, such an assessment may help to establish the functional significance of abnormalities observed in the coronary angiogram\[37\]. For example, in a patient with both complete obstruction of one coronary vessel (and possibly previous myocardial infarction) and a moderately severe stenosis in another vessel, perfusion scintigraphy may help to decide whether symptoms are likely to be alleviated by percutaneous intervention (PTCA) of the moderately severe lesion only, or by surgical intervention of both vessels.

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Table 1(a) Pretest likelihood of coronary artery disease in symptomatic patients according to age and sex

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Typical angina</th>
<th>Atypical angina</th>
<th>Non-anginal chest pain</th>
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<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
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<tr>
<td>30–39</td>
<td>69.7 ± 3.2</td>
<td>25.8 ± 6.6</td>
<td>21.8 ± 2.4</td>
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<tr>
<td>40–49</td>
<td>87.3 ± 1.0</td>
<td>55.2 ± 6.5</td>
<td>46.1 ± 1.8</td>
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<td>50–59</td>
<td>92.0 ± 0.6</td>
<td>79.4 ± 2.4</td>
<td>58.9 ± 1.5</td>
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<tr>
<td>60–69</td>
<td>94.3 ± 0.4</td>
<td>90.1 ± 1.0</td>
<td>67.1 ± 1.3</td>
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</tbody>
</table>

Table 1(b) Coronary artery disease post-test likelihood (%) based on age, sex, symptom classification and exercise-induced electrocardiographic ST-segment depression

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>ST depression (mV)</th>
<th>Typical angina</th>
<th>Atypical angina</th>
<th>Non-anginal chest pain</th>
<th>Asymptomatic</th>
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<td>30–39</td>
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<td>25</td>
<td>7</td>
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<td>0.05–0.09</td>
<td>68</td>
<td>24</td>
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<td>0.10–0.14</td>
<td>83</td>
<td>42</td>
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<td>0.20–0.24</td>
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(3) A further option is to proceed immediately from history, physical examination and ECG to coronary angiography. This approach may be indicated particularly in patients with typical and severe symptoms, including unstable angina, patients with early post infarction angina, and in patients with early recurrence of symptoms after previous coronary intervention\[36\].

In clinical practice, the second approach is followed most frequently. In patients with frequent or severe stable angina, functional assessment is often useful prior to or in addition to angiography. It should be appreciated that symptoms resembling angina do not necessarily have a causal relation to any coronary artery narrowings present. Thus, additional functional assessment may be needed in patients with less typical symptoms and moderately severe coronary artery narrowings. Furthermore, such an assessment may help to establish the functional significance of abnormalities observed in the coronary angiogram\[37\]. For example, in a patient with both complete obstruction of one coronary vessel (and possibly previous myocardial infarction) and a moderately severe stenosis in another vessel, perfusion scintigraphy may help to decide whether symptoms are likely to be alleviated by percutaneous intervention (PTCA) of the moderately severe lesion only, or by surgical intervention of both vessels.
In patients without previous diagnosis of coronary artery disease, a stepwise approach can be followed to assess the probability of significant coronary artery disease based on a combined analysis of factors such as age, gender and the type of chest pain, as well as presence and degree of ST segment changes during exercise (Tables 1 (a) and (b)). The probability of the presence of significant coronary artery disease can be refined by analysis of the presence and degree of ST segment changes during exercise[38,39]. From the Table it is apparent that an exercise test will not be very useful to verify the diagnosis of coronary artery disease in a 64-year-old man with typical angina. Even in the absence of ECG changes during the test, the likelihood of coronary artery disease will still be 79%, while it would rise to 99% if 0.2mV ST segment depression were to occur. Yet the test may help to determine the functional impairment of that patient (exercise tolerance), to measure the blood pressure response (as an indicator of left ventricular function) and to estimate prognosis. Similarly, the diagnostic value of exercise electrocardiography is low in asymptomatic men and women.

The greatest diagnostic value is obtained in patients with an intermediate pre-test likelihood, for example between 20% and 80%. A further refinement is a multivariate analysis of stress test results[40,41], in which the probability is estimated based on a combination of heart rate at peak exercise, ST segment depression, the presence or absence of angina during the test, workload achieved and ST segment slope. Such estimation of the likelihood of coronary artery disease provides more insight into the actual situation of a patient than an arbitrary classification of normal or abnormal.

In patients with a low probability of coronary artery disease (for example, <20%) and an adequate exercise tolerance, usually no further investigations will be necessary, even though the presence of coronary artery disease can not be excluded. In patients with a high post test likelihood (for example >80%) the diagnosis of coronary artery disease has been established. If the symptomatology is moderately severe or severe, and not adequately controlled by medical therapy, coronary angiography is intended to determine whether coronary intervention is warranted.

In patients with an intermediate post test likelihood (between 20 and 80%) after a stress test, a second non invasive test will be helpful to distinguish between subgroups of patients with a higher or lower post test probability. Depending on facilities and experience in a given environment, either myocardial perfusion scintigraphy or stress echocardiography may be chosen as a second test (Table 2).

In principle, subsequent tests to improve diagnostic certainty should be requested only if the results would impact on patient management, including prescription of preventive measures. Often, no further tests are required in patients with mild symptoms and a normal exercise tolerance, even if the diagnosis remains somewhat uncertain. In contrast, additional stress test or angiography is warranted in patients with more severe or frequent symptoms, particularly if these occur at low workload in the absence of electrocardiographic signs of myocardial ischaemia. Additional stress tests with perfusion scintigraphy or echocardiography are often useful in:

1. Patients with typical anginal symptoms and non-diagnostic exercise ECG (ECG changes at rest because of left ventricular hypertrophy, pre-excitation or bundle branch block) or difficulty in performing exercise due to non-cardiac limitations, or a normal exercise ECG with (moderately) severe symptoms.

2. Subjects with atypical angina or absence of symptoms with a positive exercise ECG (with the exception of very abnormal changes).

3. Special subgroups with typical angina and a positive exercise ECG where false-positive stress tests are common, for example in younger women[42].
It should be appreciated that the diagnostic approach to patients with chest pain of possible cardiac origin has changed since the introduction of effective measures for prevention of progression of coronary artery disease. In addition to an advice to stop smoking and treatment of hypertension and diabetes, patients with known coronary artery disease may now require treatment with lipid lowering drugs, particularly cholesterol synthesis inhibitors (statins). It has been shown unequivocally that these drugs reduce the rate of progression of coronary disease and reduce the incidence of coronary events. Since these drugs are costly, these should be prescribed for (secondary) prevention only in patients with documented coronary disease. Thus, it has become important to establish or rule out this diagnosis even in patients with mild symptoms in whom coronary intervention would not be considered.

Non-invasive investigations

Resting electrocardiogram (ECG)

All patients with the suspicion of angina pectoris based upon symptoms should have a resting 12-lead electrocardiogram (ECG) recorded. This will not identify with certainty whether patients have coronary artery disease or not; a normal resting ECG is not uncommon even in patients with very severe angina. However, the resting ECG may show signs of coronary artery disease such as previous myocardial infarction or an abnormal repolarisation pattern. In addition, the ECG may show other abnormalities such as left ventricular hypertrophy, bundle branch block, pre-excitation, arrhythmias or conduction defects. Such information may be helpful in defining the mechanisms responsible for chest pain or in identifying patient subgroups with a higher risk of death or myocardial infarction.

ECG stress testing

For patients with stable angina pectoris, the first investigation after clinical assessment and a resting ECG is likely to be an exercise ECG. The exercise test should be carried out only after careful clinical evaluation of symptoms and a physical examination including resting ECG. ECG changes during exercise are associated with the presence of coronary artery disease with a sensitivity of around 70% and a specificity of approximately 90%. The results of the ECG stress testing should be interpreted by trained clinicians. In population studies with a low prevalence of ischaemic heart disease the proportion of false positive tests will be high. Furthermore, false positive exercise recordings are common in women with a low prevalence of disease. ECG changes during exercise suggesting myocardial ischaemia in the absence of coronary artery disease are also seen in patients with such conditions as syndrome X, digitalis treatment and electrolyte abnormalities.

In order to improve the specificity and sensitivity of exercise ECG to identify coronary artery disease the test procedure should be standardized with the use of nomograms predicting the exercise response taking into account age, gender and body size. The test may be conducted in patients taking anti-ischaemic drugs. A ‘normal’ test in such patients does not rule out significant coronary disease. Thus, a second test, with less or no medication, may be indicated, depending on the clinical question to be answered.

The evaluation of the exercise test demands assessment of the pretest and post-test likelihood of coronary disease in the particular patient under investigation (Table 1 (a) and (b)). The ECG should be continuously recorded with a print-out of signal averaged recordings at preselected intervals, mostly at each minute during exercise, and 4 to 10 minutes of recovery after exercise. An exercise test is commonly regarded as ‘positive’ if there is horizontal or downsloping ST-segment depression 0.1 mV in any lead. Such a dichotomous approach (i.e. ‘positive’ or ‘negative’) is to be deplored. It is misleading because in assessing the significance of the test, one should take into account not only the ECG changes but also the work load, heart rate increase and blood pressure response, and the clinical context. ST changes related to heart rate have been suggested to be more reliable, describing the slope of ST segment changes over time. Either the Bruce protocol or one of its modifications on a treadmill or a bicycle ergometer can be employed. The bicycle work load is described in terms of Watts (W). Increments are of 20 W per 1 minute 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. A standard protocol should be employed, since this may be used for future reference in the same patient. In addition to the diagnostic value of the exercise ECG, the stress test has an important role in demonstrating silent ischaemia and in predicting the prognosis of patients with chronic stable angina pectoris and following the progress of the disease or the effect of treatment.

The reason for stopping the test and the symptoms at that time, including their severity, should always be recorded. Time to the onset of ECG changes and/or symptoms, the overall exercise time, the blood pressure and heart rate response, and the post-exercise recovery pace of ECG changes should be assessed. The exercise stress test is terminated at the discretion of the physician for one of the following reasons:

1. Symptom limitation, e.g. pain, fatigue, dyspnoea; for repeated exercise tests. The use of Borg scale is recommended to allow comparisons.
2. Combination of symptoms such as pain with significant ST-changes.
3. Safety reasons such as marked ST-segment changes (particularly ST-segment elevation), arrhythmias, or a sustained fall in systolic blood pressure.
**Ambulatory monitoring**

The sensitivity and specificity of the ST segment changes for the diagnosis of coronary artery disease are lower than for the exercise test, but may reveal evidence of myocardial ischaemia that is not provoked by exercise\[^{52,53}\]. Ambulatory electrocardiographic (Holter) monitoring rarely adds important clinical information for assessment of the diagnosis of chronic stable angina pectoris over and above that provided by an exercise test. Evaluation of repolarisation changes by ambulatory monitoring requires the use of equipment with an adequate frequency response, according to the guidelines for electrocardiography. Two-lead or three-lead recordings are used most frequently and should include a bipolar V5 chest lead. Recording of twelve-leads by ambulatory monitoring may have advantages.

**Echocardiography at rest**

Two-dimensional echocardiography is useful to estimate the size of the heart chambers and regional and global left ventricular function. In addition, M Mode echocardiography offers accurate and reproducible measurements of cardiac chamber dimension and wall thickness, although the geometry in patients with coronary artery disease is often complex due to myocardial infarction, remodelling and aneurysms. Measurements of left ventricular performance during systole and diastole may include ejection fraction, ejection time intervals, and systolic and diastolic volumes, wall stress, stroke volume, cardiac output and the diastolic Doppler flow pattern. Echocardiography is also useful to rule out the possibility of other disorders such as valvular heart disease or hypertrophic cardiomyopathy as a cause of symptoms\[^{54}\].

**Stress echocardiography**

Stress echocardiography has been developed as an alternative to ‘classical’ exercise testing with electrocardiography, and as an additional investigation to establish the presence or location of myocardial ischaemia during stress.

At least 10 to 20% of patients referred for evaluation of chest pain are unable to perform an adequate diagnostic ECG exercise test. In these patients dobutamine stress echocardiography represents an alternative exercise independent stress modality. Yet it should be appreciated that 5% of patients have an inadequate echo window and 10% of the patients referred for a dobutamine stress test have a non-diagnostic result (submaximal negative test).

The methodology and interpretation of stress echocardiography has been described in several excellent reviews\[^{55,56}\]. In short, the heart is stressed by infusion of dobutamine or similar substances. Dobutamine is administered intravenously starting at 10 μg kg\(^{-1}\) min\(^{-1}\) for 3 min, increasing by 10 μg kg\(^{-1}\) min\(^{-1}\) every 3 min to a maximum of 40 μg kg\(^{-1}\) min\(^{-1}\), which is continued for 6 min. In patients not achieving 85% of their age-predicted maximal heart rate, who have no symptoms or signs of ischaemia, atropine is given at the lower stage (0·25 mg injections to a maximum of 1·0 mg) while dobutamine is continued. Throughout the test the ECG is monitored, and full 12 lead ECG recordings are made every minute. The two-dimensional echocardiogram is continuously monitored on a quad screen display for side by side examination of rest and stress images, and recorded by video, or on digital equipment. Normal myocardium shows an increase of movement and thickening during stress, while ischaemia is recognized by reduced regional wall thickening and transient regional wall motion abnormalities.

It should be appreciated that proper interpretation of changes in wall motion on a stress echocardiogram requires considerable, experience and expertise. Optimal recording equipment and computer display (quad screen) is essential. In experienced hands this method can become an excellent tool to clarify regional wall motion abnormalities due to coronary disease.

**Myocardial perfusion scintigraphy**

Myocardial perfusion scintigraphy is usually performed in association with a symptom limited exercise test on either a bicycle ergometer or a treadmill. It offers a somewhat more sensitive and specific prediction of the presence of coronary artery disease than exercise electrocardiography and allows detection of the location of myocardial ischaemia during exercise. Isotopes used most frequently are thallium 201 and technetium-99 m labelled perfusion tracers. The isotope is injected at peak exercise, preferably at the time when a patient experiences symptoms compatible with myocardial ischaemia. Images are made immediately (thallium) or shortly after exercise and repeated a few hours later, or the next day after a new injection of the tracer. In patients who are unable to exercise adequately, infusion with dobutamine or similar agents may be used to stress the heart. A third approach is the use of vasodilators (dipyridamole or adenosine) to enhance perfusion in areas supplied by ‘normal’ coronary arteries.

Myocardial ischaemia, or underperfused areas after vasodilatation, can be recognized as an area with diminished isotope uptake during exercise in comparison with the uptake at rest. Interpretation of the test can be facilitated by semi-quantitative analysis and tomographic display (SPECT= single photon emission computer tomography). Sensitivity and specificity for perfusion scintigraphy are similar to those obtained with stress echocardiography. Increased uptake of thallium 201 in the lung field identifies patients with extensive coronary artery disease\[^{57-60}\].
Radionuclide angiography during exercise

Radionuclide angiography using technetium labelled red blood cells can be used to assess left ventricular function (global ejection fraction and regional wall motion) at rest and during exercise. For these studies exercise is conducted in the supine position with stepwise increments in work load with a 3 to 5 min step duration. Images are collected over 1 to 2 min on each exercise stage. Healthy subjects will show a normal ejection fraction at rest which increases on exercise, while patients with coronary disease (or other types of left ventricular dysfunction) often exhibit no increase or a decrease of global ejection fraction as well as development of regional wall motion abnormalities during exercise[57,58].

Coronary angiography

Coronary angiography has a pivotal position in the management of patients with chronic stable angina pectoris. It is currently the most reliable tool to ascertain the anatomial severity of coronary artery disease. However, necropsy and ultrasound studies[61] have clearly demonstrated that the extent of plaque mass is grossly underestimated by this technique. It carries a small risk of mortality (<0·1%)[62] and often needs to be supplemented by functional tests.

Indications. Taking into account the development of new techniques of myocardial revascularization and the low risk of complications of coronary angiography, it should be considered in the following conditions:

1. Severe stable angina (Class 3 of the Canadian Cardiovascular Society Classification (CCS)), particularly if the symptoms are inadequately responding to medical treatment;
2. Chronic stable angina (Class 1 to 2) if there is a history of myocardial infarction or evidence of myocardial ischaemia at a low work load;
3. Chronic stable angina in patients with bundle branch block if readily-induced ischaemia is demonstrated by myocardial perfusion scintigraphy;
4. Patients with stable angina who are being considered for major vascular surgery (repair of aortic aneurysm, femoral bypass, or carotid artery surgery);
5. Patients with serious ventricular arrhythmias;
6. Patients previously treated by myocardial revascularization (PTCA or CABG) who develop recurrence of moderate or severe angina pectoris;
7. When it is essential to establish the diagnosis for clinical or occupational reasons.

The performance and interpretation of coronary angiography must be irreproachable. A complete examination includes left ventricular cineangiography performed in the right anterior oblique projection together with a ventriculogram in the left oblique projection. This permits assessment of left ventricular function including wall motion abnormalities. The left coronary artery is usually examined in five projections, to ensure optimal assessment of each specific coronary segment, and the right coronary artery in at least two projections. Recording of overlapping segments must be avoided and specific, steeply angulated caudal left and right anterior oblique projection must frequently be used. Interpretation of the arteriogram includes description of the morphology and severity of coronary lesions, together with the presence of collateral vessels.

Most angiographers tend to overestimate the degree of stenosis prior to intervention, and underestimate the residual narrowing after treatment[63,64]. Quantitative coronary angiography greatly improves the accurate assessment of coronary stenoses. In clinical practice, assessment and, even more, the treatment of a 50–75% stenosis must be complemented by evaluation of its physiological importance with the usual markers of ischaemia. In a diffusely narrowed and/or small vessel, it is preferable not to use the percentage of stenosis but to use the absolute value (mm) of the minimal lumen diameter (MLD). In general, an MLD<1 mm in a proximal vessel indicates a flow-limiting stenosis, regardless of the percentage diameter stenosis.

In conclusion, coronary angiography has evolved into a routine examination. It provides a considerable body of information for establishing the diagnosis and assessing the prognosis of coronary artery disease. Nevertheless, the decision to perform this examination must be based on the clinical and physiological findings derived from a careful review of the history and evidence of myocardial ischaemia.

In selected patients, objective intravascular ultrasound may provide additional information regarding the status of plaques and the presence or absence of intracoronary thrombosis. The measurement of fractional flow reserve[65] is a promising new technique for assessment of the functional significance of stenoses. These methods are still under investigation.

TREATMENT

Aims of treatment

● To improve prognosis by preventing myocardial infarction and death
In order to achieve this end, attempts must be made to induce regression or halt progression of coronary atherosclerosis, and to prevent complications, especially thrombosis. Lifestyle changes and drugs play a vital role in this, but the myocardium may also be protected if its perfusion is enhanced by interventional techniques.

● To minimize or abolish symptoms
Lifestyle changes, drugs, and interventional techniques all play a part.
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, angina improves with proper management. Risk factors, especially smoking habit and lipid levels, should be assessed in all cases. Particular attention must be paid to elements of the lifestyle that could have contributed to the condition and which may influence prognosis. The recommendations of the European Task Force[66] on ‘Prevention of Coronary Heart Disease in Clinical Practice’ should be followed.

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[67,68]. Cessation of smoking greatly improves both symptoms and prognosis. Patients often require special help in abandoning their addiction, and transdermal nicotine has proved effective and safe in helping patients with coronary artery disease to quit smoking.

Diet. Patients should be encouraged to adopt a ‘Mediterranean’ diet, with vegetables, fruit, fish and poultry being the mainstays. The intensity of change needed in the diet depends upon the total (LDL) plasma cholesterol level and other lipid abnormalities[69]. Those who are overweight should be put on a weight reducing diet. Alcohol in moderation may be beneficial[70], but excessive consumption is harmful, especially in patients with hypertension or heart failure.

Hypertension, diabetes and other disorders. Concomitant disorders should be managed appropriately. Particular attention should be given to control of elevated blood pressure and diabetes mellitus. Both increase the risk of progression of coronary disease, particularly when ill-controlled. Also anaemia, if present, should be corrected.

Physical activity. Physical activity within the patient’s limitations should be encouraged, as it may increase exercise tolerance[71], and 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[72].

Psychological factors. While the role of stress in the genesis of coronary artery disease 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[73].

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 nor emotionally demanding. Nitroglycerin prior to intercourse may be helpful.

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 patients with chronic stable angina

Pharmacological treatment of angina encompasses both the prevention of the complications of coronary atherosclerosis and the relief of symptoms.

The prevention of myocardial infarction and death
In recent years, it has become clear that drugs that modify lipids or decrease the risk of thrombosis substantially improve prognosis with regard to the incidence of both myocardial infarction and death. Nitrates and calcium antagonists have not been shown to be effective in this respect, but large trials have established that, at least in the post-infarction patient, betablockers reduce mortality and reinfarction.

Lipid-lowering drugs. All patients with angina pectoris should have a lipid profile. The Scandinavian Simvastatin Survival Study[85] showed that a statin, given to patients with angina pectoris and a total cholesterol level between 5-5 and 8-0 mmol. l⁻¹ (212 and 308 mg. dl⁻¹), substantially reduces the risk of myocardial infarction, death, and the need for coronary bypass surgery. Supportive evidence from other trials suggests benefit at even lower lipid levels[46,47]. Previous concerns about the risks of lipid-lowering have now been allayed. Indications for drug therapy depend upon the overall risk of the patient[66,74]. If diet fails to reduce the cholesterol level, lipid-lowering drugs should be prescribed with the aim of reducing the total cholesterol level to below 5-0 mmol. l⁻¹ (192 mg. . dl⁻¹) and LDL cholesterol below 2-6 mmol. l⁻¹ (100 mg. . dl⁻¹). The choice of lipid-lowering regimen will depend upon the lipid-profile.

Aspirin. An overview of trials of antiplatelet agents in 3000 patients with stable angina showed a 33%
reduction in vascular events\textsuperscript{75,76}. It is recommended that aspirin is administered routinely in a dosage of 75–160 mg daily in the absence of contra-indications.

**Hormone replacement therapy (HRT).** Epidemiological evidence strongly suggests a beneficial effect of HRT in patients without manifest coronary disease. Although there is little information on the benefits and safety of HRT in anginal patients, there is no reason not to use these drugs where indicated in patients with coronary artery disease.

**Anti-oxidants.** The theoretical benefits of anti-oxidant therapy have not yet been confirmed in adequate trials. Further studies are needed before this therapy can be recommended for angina patients.

**Drugs for symptom relief**

Three main classes of drugs are used to control symptoms in chronic stable angina: nitrates, beta-blockers and calcium antagonists\textsuperscript{77}. Given in appropriate regimens, all these agents can be effective in this context, but there is a considerable and, to a large extent, unpredictable variation in response and adverse effects. The aim of anti-anginal treatment is to reduce the myocardial oxygen requirements or to increase myocardial perfusion. Often, it may be possible to achieve both aims.

**Nitrates.** Sublingual nitrates work rapidly, i.e. within minutes, and the effect lasts for about 30–45 min. Profound relief of symptoms is the result of venodilation, afterload reduction and coronary dilatation. Many nitrate delivery systems have been developed for chronic prophylactic use. It has become clear, however, that patients can develop at least partial tolerance to this therapy. The use of nitrate-free interval between dosing is an effective means of overcoming the development of tolerance, although in some cases a rebound of symptoms may occur at this time. This can be obviated by the concomitant use of another class of anti-anginal agent. Nitrates did not influence morbidity or mortality in the 4–6 weeks after myocardial infarction in the ISIS-4\textsuperscript{78} and GISSI-3\textsuperscript{79} trials. There have been no long-term trials of nitrates in patients with chronic stable angina.

The main adverse effect of nitrates is headache, which may be troublesome but tends to diminish with continued use. Other side-effects include flushing and syncope. Nitrates are particularly indicated for the prompt relief or prevention of angina and are also of value long-term in patients with heart failure or with contra-indications to beta-blockers. They are often (but not always) effective in patients with vasospastic angina and in syndrome X.

**\(\beta\)-blockers.** \(\beta\)-blockers act mainly by blocking the \(\beta_1\) receptor. ‘Non-selective’ \(\beta\)-blockers also block the \(\beta_2\) receptor but even ‘selective’ \(\beta\)-blockers have some effect upon this receptor, especially at higher dosages. Blockade of the \(\beta_1\) receptor slows the heart rate and reduces myocardial contractility; both these effects reduce myocardial oxygen demand and thereby the severity of ischaemia. All \(\beta\)-blockers when given in adequate dosages help to prevent anginal attacks.

Selective \(\beta\)-blockers are generally to be preferred in patients suffering from asthma, peripheral vascular disease and insulin-dependent diabetes, although they are not entirely safe in these contexts. Some more recently developed agents cause peripheral vasodilatation and may be more useful in cases of peripheral vascular disease. Major adverse effects include severe bradycardia, hypotension, bronchospasm and, rarely, heart failure, but these are uncommon if patients are appropriately selected. More subtle side-effects, which may go unrecognised unless sought, include fatigue, lassitude, nightmares, and cold extremities.

The effect of \(\beta\)-blockers on the prognosis of stable angina has not been specifically studied in a large trial. A history of angina has, however, been present in about one-third of the patients recruited into post-infarction studies of these agents. The Beta-Blocker Pooling Project\textsuperscript{80} reported a highly significant reduction in mortality in this sub-group, and it seems reasonable to assume that \(\beta\)-blockers have the potential to prevent death, especially sudden death, and the development of myocardial infarction even when there has been no prior infarction.

\(\beta\)-blockers are indicated for most patients with more than the mildest angina, in the absence of contra-indications. They are particularly indicated in the post-infarction patient.

**Calcium antagonists.** Calcium antagonists cause coronary and peripheral vasodilatation. Furthermore, smooth muscle relaxation and reduction of afterload together with the negative inotropic effects of some of the agents will reduce myocardial oxygen consumption. While various formulations of the two prototype papaverine-like and benzothiazepine-like calcium antagonists — verapamil and diltiazem — are widely available, most current development involves analogues of the nifedipine-like dihydropyridine class. The calcium antagonists are a structurally heterogeneous group of compounds with important differences in pharmacological action.

Verapamil slows conduction through the atrioventricular node and has important negative inotropic effects as well as causing smooth muscle relaxation which leads to an increase in coronary blood flow and a reduction in afterload. The dihydropyridines, such as nifedipine and amlodipine, also cause smooth muscle relaxation but have no effect on cardiac pacemaker tissue which may result in a reflex increase in the heart rate. In common with other calcium antagonists, these drugs have negative inotropic effects, which are, however, less marked than those of verapamil. The effect of diltiazem is similar to those of verapamil though it has a less potent effect of left ventricular function.

The calcium antagonists in general should be used with caution in patients in heart failure or with...
poor left ventricular function, although some long acting dihydropyridines, such as amiodipine, may be safer in this context.

Unlike β-blockers, calcium antagonists have not been shown to reduce mortality after myocardial infarction, although there is some evidence that verapamil and diltiazem may reduce the risk of reinfarction[81,82]. Concerns have been expressed about the safety of calcium antagonists, particularly the short-acting preparations[83]. Calcium antagonists should be considered if β-blockers are contra-indicated or ineffective. They are specifically indicated for vasospastic angina.

Other agents. Molsidomine belongs to a newly discovered class of sydnonimines, which resemble nitroglycerin in their mode of action. Molsidomine appears to act more slowly than nitrates, but its effect lasts longer. Nicorandil, a potassium channel activator, also possesses nitrate-like activity. It relaxes vascular smooth muscle; and does not appear to cause tolerance with chronic dosing. Metabolic agents, such as trimetazidine, may also be useful.

Combination treatment. Many but by no means all studies have demonstrated additional beneficial anti-anginal effects when a β-blocker is used in combination with a calcium antagonist or a long-acting nitrate preparation. Care needs, to be taken however, with the combination of a β-blocker and verapamil or diltiazem, especially if there is evidence of conduction disturbance or left ventricular dysfunction. Furthermore, calcium antagonists may be combined with long-acting nitrates.

The effects of combining drugs may be due to an additional reduction in the rate-pressure product both at rest and on exercise, but the IMAGE study[84] suggests that the benefit of adding a new agent may be due to the recruitment of new responders than to combination per se. In addition, synergy between two classes of drug may abollish the potentially detrimental effects of each. There is little evidence to support the current vogue of using triple therapy. Indeed as Tolins et al[85] have emphasized, ‘maximal’ therapy is not necessarily optimal therapy.

Choice of anti-anginal agent. All patients should be offered short-acting nitrates either sublingually or by spray. These drugs may be used not only to treat an acute episode but are particularly valuable taken prophylactically when an attack is anticipated, for example prior to exercise.

Choice of first line treatment for prophylaxis depends on the underlying predominant pathophysiological process, left ventricular function, and associated conditions. Patients with very clear-cut effort-related angina should be offered a β-blocker as should those with a prior myocardial infarction. Diltiazem and verapamil are also useful in such circumstances though they should be avoided in the presence of significant left ventricular dysfunction. Nitrates are of value where there is left ventricular dysfunction; β-blockers and some vascular selective long-acting dihydropyridines can also be given cautiously in such circumstances. Patients with asthma and peripheral vascular disease may be best treated with a long acting nitrate or a calcium antagonist, although selective β-blockers may be given with caution. As mentioned above, various combinations of β-blockers, nitrates and calcium antagonists have been shown to be useful where a single agent is ineffective, but it is probably best to evaluate an alternative single drug before starting combination treatment.

Percutaneous transluminal coronary angioplasty

Percutaneous transluminal coronary angioplasty (PTCA) is widely used in the treatment of stable angina pectoris. Introduced in 1977 by Grünzig, the number of procedures has increased exponentially and angioplasty has surpassed the frequency of coronary bypass graft surgery (CABG). This dramatic increase is largely the result of major changes in the technique, the materials, and lesion selection criteria. The introduction of better imaging systems has also contributed to the great improvements in results that have been seen. In the majority of cases, the procedure is achieved with a balloon tracking over a guide wire. Alternative methods may be preferred for particular types of lesions. Large bulky, eccentric lesions are good indications for directional atherectomy. Ablation with a Rotablator is more effective in the treatment of hard, fibrocalcific lesions, ostial lesions, and diffuse disease. Earlier enthusiasm for laser therapy has declined because of the frequent need for adjunctive balloon angioplasty and a high rate of restenosis. By contrast, stents are used more and more frequently in coronary interventional cardiology. Better deployment and new management after stent implantation have increased the safety of coronary stenting and led to a low risk of subacute thrombosis and vascular complications[86]. Stents have markedly decreased the need for emergency CABG, the rate of post procedure myocardial infarction, and restenosis.

Success and risks. In stable angina pectoris, a procedural success in anatomically suitable patients is achieved in 95% of cases[87]. The mortality rate is less than 0.2% in patients with single vessel disease and 0.5% in case of multivessel disease. The need for emergency bypass surgery is currently less than 1% since the advent of stents. The rate of myocardial infarction, as recognised by developments of new Q waves, is now less than 1%.

These results can be achieved within a short period of hospitalisation. Furthermore, the use of small (6 F) catheters allow simple lesions to be treated on a day case basis. The return to work is rapid.

Restenosis. Restenosis remains a major concern. It occurs in 35 to 40% of cases with angiographic control. In some cases, restenosis is detected by the recurrence of symptoms but it can be completely silent and detected.
only by systematic angiography. Non-invasive tests are not very predictive (predictive value 50% if positive) but have a good negative predictive value (93%).

There are two principal mechanisms of restenosis: chronic recoil of the artery (remodelling) and neo-intimal proliferation (healing process). In more than 50 randomised multicentre trials, drugs have failed to prevent neo-intimal proliferation perhaps because they attacked only one (relatively limited) of the mechanisms. Recently, trials with c73E3 Gp IIb/IIIa receptor blockade have indicated a reduction in death and myocardial infarction after PTCA. The remodelling process can be prevented by stent implantation which significantly decreases the rate of restenosis in patients with stable angina and vessels with diameters between 2.6 and 3.4 mm. The combination of stent implantation and a drug locally or generally delivered could lead in the near future to a marked reduction in the rate of restenosis. When the patient experiences recurrence of chest pain and significant restenosis, a repeat PTCA with or without stent implantation can be performed. The risk of this reintervention is low and the success rate high.

Comparisons of PTCA and drug treatment. There is, as yet, no convincing evidence that PTCA is superior to medical treatment with regard to the risk of myocardial infarction or death in patients with chronic stable angina. The decision whether to undertake PTCA in such patients depends, therefore, on the anticipated benefit to be obtained in respect of angina. Few comparative trials have been undertaken to address this issue. In the ACME trial, a randomized study comparing PTCA vs medical therapy in single LAD disease, PTCA decreased the incidence of symptomatic ischaemia and was associated with more normal treadmill exercise tests. However, 48% of the medically treated patients were rendered free of angina compared with 64% of the PTCA group, and PTCA was associated with a higher frequency of complications and greater expense.

Coronary bypass graft surgery

Coronary bypass graft surgery has been recognised as a very effective method of myocardial revascularisation for more than 25 years. Coronary artery surgery is now a reproducible and technically precise procedure. Patient survival and freedom from events are dependent to an important degree on attention to technical details. The coronary bypass operation is usually performed with cardiopulmonary bypass using the pump oxygenator, although less invasive techniques are being increasingly employed. A number of methods of minimising perioperative ischaemia and numerous strategies for myocardial management are in use.

Conduits for coronary bypass graft surgery. Several autogenous conduits are available. The long saphenous vein is still widely used, but if possible, arterial grafts are preferred because their long-term patency is superior to that of saphenous vein graft. The left internal mammary artery is incorporated in almost all bypass procedures of the left coronary artery. The right internal mammary artery, may also be used. Other conduits, such as the right gastro-epiploic artery and inferior epigastric artery may also be considered. Endarterectomy is most often reserved for vessels with distal disease not satisfactory for distal grafts. This method is most commonly applied to the right coronary artery at and beyond the crux. It has been shown that endarterectomy is associated with a higher perioperative mortality and myocardial infarction whilst a lower long-term graft patency is frequently observed.

Risks and complications. The in-hospital major complications largely depend on the extent of vessel disease, left ventricular function and associated diseases (renal or respiratory insufficiency). The in-hospital mortality rate is 1% in single vessel disease and increases up to 4 to 5% in multivessel disease with poor left ventricular function. Perioperative myocardial infarction characterized by the occurrence of new Q waves may be observed in 4 to 5% of cases.

Patency of the conduits. The patency rate of saphenous vein grafts is quite variable but 10 to 20% of grafts are occluded within one week of surgery from thrombosis. By 3 to 5 years after operation, 60–70% of vein grafts have evidence of atherosclerotic narrowing. This new disease is characterized by very soft, friable material which is very prone to embolize to the distal part of the vessels. By contrast, 90% of the internal mammary artery grafts anastomosed to the left anterior coronary artery are patent 10 years after operation. The risk of re-operation is high, the 5 to 11% mortality rate depending mainly on the LV function.

Comparison of CABG with medical therapy. Yusuf et al. have undertaken a systematic review of the outcomes of 2649 patients randomly assigned to receive CABG or medical management for coronary artery disease in seven individual trials conducted between 1972 and 1984. This meta-analysis demonstrated that CABG reduced mortality in patients with left main disease and others at relatively high risk, such as those with three vessel disease associated with impaired left ventricular function.

Comparison of PTCA vs CABG. Five major randomised trials have compared these two forms of intervention, mainly in patients with multiple vessel disease. Three were conducted in Europe (RITA, GABI and CABRI) and two in U.S.A. (EAST and BARI). Only one (RITA) compared the results of PTCA and CABG in patients with single vessel disease.

The results of these trials are uniform and consistent: both methods of myocardial revascularization were associated with a similar risk of death and non-fatal myocardial infarction, although the trials were
underpowered to detect small differences between both methods or differences among specific patient subgroups. CABG involved a longer hospitalization and convalescence but thereafter, patients had less angina and required fewer anti-anginal drugs. PTCA is a simpler method, without thoracotomy, general anesthesia, or exposure to nosocomial infection, but, subsequently, patients, particularly women, were more likely to complain of angina, take anti-anginal drugs and undergo further revascularization procedures. In the BARI trial, treated diabetics (insulin or oral therapy) had a significantly lower 5-year mortality rate with CABG than with PTCA (19% versus 35% P<0.02). In contrast, the mortality rate in diabetics not on drug treatment was 9% for both therapies. Over 2 years, the cost of a treatment policy commencing with PTCA is around 80% of a policy based on CABG. In evaluating these studies, it has to be borne in mind that all are relatively short term, and that in the long-term further interventions are likely to be necessary in both groups as native vessel coronary disease progresses. The high risk of repeat CABG may then become an important issue, while angioplasty should be considered as a repeatable low risk procedure.

**The choice of treatment in stable angina pectoris**

In selecting a treatment programme for patients with stable angina pectoris, the physician must constantly bear in mind the two aims of treatment — to improve prognosis and to relieve symptoms. This strategy is based on four pieces of information: a careful history, the response to some form of stress testing, ventricular function, and the extent of coronary artery disease. Other factors have obviously to be taken into consideration, such as age, gender, and comorbid conditions (pulmonary or renal disease, for example).

**General management.** It must be stressed that all patients, whether or not they are candidates for intervention, should adopt those lifestyle changes that improve prognosis such as stopping smoking and a lipid-modifying diet. Aspirin should be given as a routine in the absence of contra-indications, and lipid-modifying drugs should be added if cholesterol remains high in spite of a diet.

**Medical treatment vs intervention.** When first seen and regularly thereafter, the physician should consider whether the patient is at high risk of death. If so, and if investigations show that the prognosis would be improved by surgery, this should be undertaken, irrespective of the severity of the symptoms. Otherwise, medical treatment should be initiated. If symptoms are not adequately controlled after some weeks of what is considered to be optimal medical management, the indications for PTCA and CABG should be reviewed.

**Choice of intervention (Fig. 1).** In deciding whether PTCA or CABG should be selected, the following considerations should be taken into account:

**High risk patients with significantly impaired LV function.** CABG is recommended in patients with poor LV function (EF <30%) and left main coronary artery disease. If the left main artery has been surgically bypassed, PTCA of that artery (with or without the help of LV assistance) may be performed. The high risk of acute and chronic recoil leading to restenosis necessitates stent implantation in this case. CABG is also recommended for a single remaining vessel. CABG is indicated for abnormal LV function and triple vessel disease, particularly when the proximal LAD is involved.

**Associated severe co-morbid conditions.** In some cases, such as severe renal failure or pulmonary insufficiency, CABG may be contraindicated. PTCA, with or without the help of a left ventricular assistance device (cardiopulmonary support), can be used.

**Patients with normal or mild impairment of LV function.** Patients with left main narrowing should be treated by surgery. Triple vessel disease including proximal LAD stenosis could be considered for CABG in most of the cases but, depending on the characteristics of the lesions and if complete myocardial revascularization is possible, PTCA could be performed. Patients with double vessel disease may be treated by coronary angioplasty, even in cases with a totally occluded vessel: Subgroup analysis of CABRI showed that in this particular group of patients, there was no difference in terms of survival or non-fatal MI between the two techniques of myocardial revascularization. Patients with single vessel disease should be treated with angioplasty rather than with CABG.

**Special subgroups**

**Women**

There is a growing awareness of coronary artery disease in women[101,102]. Especially in younger women where
coronary artery disease is assumed to be less likely, chronic stable angina pectoris may be underdiagnosed. Symptoms of chest pain in women are often atypical and therefore dismissed, particularly if the woman is young. Furthermore, because the prevalence of coronary artery disease in younger women is low, the exercise test is more likely to be falsely positive. This explains the more frequent prevalence of chest pain with normal coronary arteries in women (five times that of men) and therefore the better prognosis for women with ‘angina’ who have been evaluated without angiography as a baseline. The diagnostic value of exercise stress testing is lower in women, primarily because of the lower prevalence of coronary artery disease. Women who can exercise to stage III of the Bruce protocol or who have ST-segment normalisation within 4 min postexercise are unlikely to have coronary artery disease. Women who can exercise to stage III of the Bruce protocol or who have ST-segment normalisation within 4 min postexercise are unlikely to have coronary artery disease. Microvascular disease (syndrome X) may provoke chest pain in women due to myocardial ischaemia despite angiographically normal arteries. Women are less likely to be referred for coronary angiography than men and women referred for chest pain who subsequently underwent coronary angiography are found to have normal coronary arteries more often than men. Due to the high frequency of false positive exercise ECG tests, myocardial perfusion scintigraphy or stress echocardiography should more often be considered. Women with typical angina symptoms on effort with positive exercise ECG or myocardial perfusion defects should have access to coronary angiography.

There is no justification for treating men and women differently after coronary artery disease is diagnosed. Women have a higher morbidity and mortality when suffering myocardial infarction than men after taking into account known adverse factors and correcting for age. There are suggestions that treatment of myocardial infarction is less vigorous in women than in men and that survival chances are reduced in women discharged after myocardial infarction because they do not have the same therapeutic interventions as men. There is a need to improve detection and treatment of coronary artery disease in women; when diagnosed they have the same benefits from medical therapy and revascularization.

The elderly

After the age of 75 years there is an equal prevalence of coronary artery disease in men and women. The disease is more likely to be diffuse and severe; left main coronary artery stenosis and triple vessel disease are more prevalent in older patients, as is depressed left ventricular function. Cooexistent illness or a sedentary lifestyle may limit the usefulness of exertional chest pain as a diagnostic finding and exercise testing is less often of diagnostic value for technical reasons. Due to the diffuse distribution of coronary artery disease, there is a higher likelihood of non-specific ECG changes during the stress test. In general, elderly patients with anginal symptoms should be evaluated and managed in the same way as younger ones. With increasing age, however, many patients are willing to accept a less well proven diagnosis of chronic stable angina pectoris and to start treatment for evaluation of its efficacy. This means that not all elderly patients need be referred for exercise stress testing, especially when noncardiac factors might limit the test.

Changes in drug bioavailability, elimination and sensitivity mean that dose modification is essential when prescribing cardiovascular drugs to elderly patients. Further issues which should be taken into account when prescribing for the elderly include risk of drug interactions, polypharmacy and compliance problems. Although evidence suggests that doctors may be reluctant to treat angina aggressively in very old patients, the usual antianginal medications are as efficacious in this patient population as in the young. On the other hand, elderly patients have a higher incidence of contraindications, complications and therapy withdrawals. Considering symptoms as well as prognosis, elderly patients have the same benefit from medical therapy, angioplasty and bypass surgery as younger patients.

Syndrome X

A significant proportion of patients undergoing diagnostic coronary angiography for chest pain show normal or near normal coronary arteries. It has been reported that 6 to 30% of the patients fall into this category. The term syndrome X is often used if patients with normal angiograms have angina-like chest pain and a positive exercise stress test. Angina with a normal coronary angiogram is clearly a heterogeneous condition and a noncardiac cause, e.g. oesophageal disease is probably common. In subsets of patients, myocardial ischaemia can clearly be provoked and a reduced coronary vasodilator reserve has been demonstrated in these patients. There are observations suggesting that patients with syndrome X may have an endothelial dysfunction.

Patients with angina pectoris and normal coronary arteries have a good prognosis regarding mortality. This is important information for the patient who often has severe chest pain, functional limitation and psychological distress. Patients with syndrome X are considered to respond poorly to conventional pharmacological treatment. Sublingual nitrates are reported to relieve chest pain in only about 50% of the patients. Conventional anti-ischaemic treatments have less consistent benefits. Since there is a female predominance in angina with normal coronary arteries and the symptoms commonly start after menopause, a pathogenetic role of oestrogen deficiency has been suggested. Hormone replacement therapy may be useful.

Logistics of care

The organisation of medical care varies greatly from one country to another, and no uniform role can therefore
be assigned to the generalist or specialist respectively. In those countries in which general practitioners or other generalists play a major role, it is important to recognise both their potential contribution and their limitations in the management of angina. Because of their usually better knowledge of the patient and his or her personal circumstances, they are often best placed to assess the whole individual and to advise on and supervise lifestyle modifications, as well as compliance with therapy. However, specialist assessment is virtually always necessary with regard to establishing the diagnosis and assessing severity and prognosis. Chest pain clinics which can review patients without delay are of considerable value, particularly in patients with recent onset or suspected unstable angina.

**Conclusions and recommendations**

1. Stable angina pectoris due to coronary atherosclerosis is a common and disabling disorder. While compatible with longevity, there is a substantial risk of progression to myocardial infarction, and/or death. With proper management, the symptoms can usually be controlled and the prognosis substantially improved. In practice, it seems probable that there is both widespread underdiagnosis and overdiagnosis, and that optimal management strategies are often not implemented.

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, an assessment of risk factors and a resting electrocardiogram. Ready access to diagnostic facilities should be available to general practitioners. Cardiology Departments should ensure that such patients are attended to without delay; some hospitals now provide a special Chest Pain clinic for this purpose.

Three diagnostic strategies may be followed depending upon patient characteristics and the severity of symptoms:

(a) The minimal assessment, as described above, without additional investigations. This may suffice, particularly in elderly patients with readily controlled symptoms, or in those disabled or seriously ill for other reasons.

(b) An initial non-invasive strategy which is appropriate for most patients. This allows an assessment of the likelihood of and the severity of coronary heart disease in patients with mild to moderate symptoms e.g. exercise testing with or without perfusion scintigraphy or stress echocardiography. In many patients, this may lead to coronary angiography.

(c) Coronary angiography without prior functional testing. This may be an option for patients with uncontrolled severe symptoms in whom revascularisation seems indicated urgently.

3. It is essential in interpreting the findings of the exercise test, that the demographic and clinical features of the individual are taken into account, as well as the workload achieved and the blood pressure and heart rate responses. While of great value in many cases, however, this test may provide equivocal or misleading information in some. Alternative investigations are needed when the diagnosis remains uncertain or functional assessment is inadequate, especially when there are electrocardiographic features which are difficult or impossible to interpret. Myocardial perfusion imaging and stress echocardiography are of particular value in demonstrating the extent and localisation of myocardial ischaemia. Echocardiography and radionuclide angiography are helpful in evaluating ventricular function.

4. 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 myocardial ischaemia in men is not so in younger women. This problem is compounded by the relatively high prevalence of ‘syndrome X’ in women, and by the frequency of ‘false positive’ exercise tests.

5. The general management of the patient is of paramount importance. This must include a strategy tailored to personal circumstances, an explanation of the nature of the condition and its treatment, and attention to lifestyle issues. Aspirin should be administered unless contra-indicated, and lipid-lowering drugs should be considered if dietary measures fail to reduce total serum cholesterol below 5·0 mmol l⁻¹.

6. Nitrates, β-blockers and calcium antagonists, alone or in combination, are effective in controlling the symptoms of angina in most cases. Because there is considerable variation in the response of patients to each class of drug, and the side-effects are unpredictable, the choice of agent should be determined on an individual basis. β-blockers are particularly indicated in those who experience angina after a myocardial infarction as they reduce the risk of reinfarction and death. The costs of the various drug regimens needs to be taken into account.

7. Coronary angiography should be undertaken when symptoms are not satisfactorily controlled by medical means, when non-invasive investigations suggest that the prognosis could be improved by angioplasty or coronary artery bypass surgery, and when it is considered essential to establish the diagnosis.

8. Percutaneous transluminal coronary angioplasty (PTCA) 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 is diminished but not abolished by stenting. There is, as yet, no evidence that PTCA reduces the risk of death.
(9) Coronary bypass graft surgery is highly effective in relieving the symptoms of stable angina and reduces the risk of death over the succeeding 10 years in particular subgroups of patients, such as those with left main stenosis, and three vessel disease, especially if left ventricular function is impaired.

(10) There is evidence that there are large numbers of patients in the community who are not being appropriately assessed and treated. Specifically, many of those with stable angina have never undergone functional testing to confirm the diagnosis and determine prognosis. Furthermore, neither lipid-lowering agents nor aspirin are being as widely prescribed as they should be.

(11) 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 PTCA and surgery should be created and maintained.

References


Appendix

Procedure of the Task Force

The Task Force on the Management of Stable Angina Pectoris was created by the Committee for Scientific and Clinical Initiatives of the European Society of Cardiology in September 1995 and asked to report to the Congress of the Society in August 1996.

The members of the Task Force were Prof. D. G. Julian (Chairman) U.K., Prof. M. E. Bertrand (France), Prof. Å. Hjalmarson (Sweden), Dr K. Fox (U.K.), Prof. M. L. Simoons (The Netherlands), Prof. L. Ceremuzynski (Poland), Prof. A. Maseri (Italy), Prof. T. Meinertz (Germany), Prof. J. Meyer (Germany), Prof. K. Pyörälä (Finland), Ass. Prof. N. Rehnqvist (Sweden), Prof. L. Tavazzi (Italy), Prof. P. Toutouzas (Greece), Prof. T. Treasure (U.K.)

A Core Group consisting of D. G. Julian, M. E. Bertrand, A. Hjalmarson, K. Fox and M. L. Simoons prepared an initial document which was circulated to the Task Force. The document was then extensively revised and circulated to the members of the Committee for Scientific and Clinical Initiatives and to the following Working Groups:

Cardiac Rehabilitation and Exercise Testing
Drug Therapy in Cardiology
Myocardial Function
Nuclear Cardiology and Magnetic Resonance
Microcirculation
Echocardiography
Coronary Circulation
Epidemiology and Prevention
Thrombosis and Platelets
Pathogenesis of Atherosclerosis
Cardiovascular Surgery
Heart Failure

After further revision, it was submitted for approval to the Committee for Scientific and Clinical Initiatives of the Society. It was also sent to Dr F. L. Ritchie of Seattle and Dr B. Gersch of Washington who kindly commented on it. The report was finalised for publication in November 1996.

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