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section 16 Cardiovascular disorders 3616 FURTHER READING Danaei G, et al. (2010). The promise of prevention: the effects of four pre- ventable risk factors on national life expectancy and life expectancy dis- parities by race and county in the United States. PLoS Med, 7, e1000248. Deloukas P, et al. (2013). Large-scale association analysis identifies new risk loci for coronary artery disease. Nat Genet, 45, 25–33. Di Angelantonio E, et al. (2009). Major lipids, apolipoproteins, and risk of vascular disease. JAMA, 302(18), 1993–2000. Di Cesare M, et al. (2013). The contributions of risk factor trends to cardiometabolic mortality decline in 26 industrialized countries. Int J Epidemiol, 42(3), 838–48. Doll R, Peto R, Boreham J, Sutherland I (2004). Mortality in relation to smoking: 50 years' observations on male British doctors. BMJ, 328(7455), 1519. Ezzati M, Riboli E (2013). Behavioral and dietary risk factors for noncommunicable diseases. NEJM, 369, 954–64. Ford ES, Caspersen CJ (2012). Sedentary behaviour and cardiovascular disease: a review of prospective studies. Int J Epidemiol, 41, 1338–53. Jousilahti P, et al. (2016). Primary prevention and risk factor reduction in coronary heart disease mortality among working aged men and women in eastern Finland over 40 years: population based observa- tional study. BMJ, 352, i721. Lopez AD, Adair T (2019). Is the long-term decline in cardiovascular- disease mortality in high-income countries over? Evidence from na- tional vital statistics. Int J Epidemiol, pii: dyz143, doi: 10.1093/ije/dyz143. Lu Y, et al. (2014). Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1.8 million partici- pants. Lancet, 383(9921), 970–83. Marmot MG, et al. (1991). Health inequalities among British civil ser- vants: the Whitehall II study. Lancet, 337(8754), 1387–93. McPherson R, Tybjaerg-Hansen A (2016). Genetics of coronary artery disease. Circ Res, 118(4), 564–78. Moore SC, et al.

(2012). Leisure time physical activity of moderate to vigorous intensity and mortality: a large pooled cohort analysis. PLoS Med, 9(11), e1001335. Mozaffarian D, et al. (2010). Effects on coronary heart disease of increasing polyunsaturated fat in place of saturated fat: a systematic review and meta-analysis of randomized controlled trials. PLoS Med, 7, e1000252. Mozaffarian D, et al. (2014). Global sodium consumption and death from cardiovascular causes. N Engl J Med, 371(7), 624–34. Rahimi K, Emdin CA, MacMahon S (2015). The epidemiology of blood pressure and its worldwide management. Circ Res, 116(6), 925–36. Rose G (1985). Sick individuals and sick populations. Int J Epidemiol, 14(1), 32–8. Roth GA, et al. (2015). Global and regional patterns in cardiovascular mortality from 1990 to 2013. Circulation, 132(17), 1667–78. Zhao D, et al. (2019). Epidemiology of cardiovascular disease in China: current features and implications. Nat Rev Cardiol, 16, 203–12. 16.13.3 Management of stable angina Adam D. Timmis ESSENTIALS Angina—the pain provoked by myocardial ischaemia—is usually caused by obstructive coronary artery disease that is sufficiently severe to restrict oxygen delivery to the cardiac myocytes. Quality of life is impaired in direct proportion to the severity of symptoms. Clinical history remains the most useful basis for diagnosis and referral decisions to specialist services, the commonest indications being (1) new-onset angina; (2) exclusion of angina in high-risk indi- viduals with atypical symptoms; (3) worsening angina in a patient with previously stable symptoms; (4) new or recurrent angina in a patient with history of myocardial infarction or coronary revascularization; (5) assessment of occupational fitness (e.g. airline pilots). Investigation—cardiac investigation is usually unnecessary in patients with nonanginal chest pain, but residual diagnostic uncer- tainty can be resolved in those with atypical or typical angina by CT coronary angiography, which is now the noninvasive test of choice. Medical treatment of angina involves (1) dealing with exacerbating comorbidities; (2) secondary prevention by lifestyle modification (smoking cessation, exercise training, Mediterranean-style diet, and so on) and drugs (aspirin, statins, and so on); (3) antianginal drugs (most com- monly β-blockers, calcium channel blockers, and short-acting nitrates). Patients with continuing moderate or severe stable angina des- pite optimal medical treatment should undergo invasive coronary angiography, particularly if they are identified as being at high risk on noninvasive testing. In symptomatic patients, revascularization is generally indicated if one or more of the major coronary arteries— or their large branches—have flow-limiting stenoses (>70% luminal narrowing) or occlusions. Percutaneous coronary intervention and coronary artery bypass grafting produce comparable symptomatic benefit. With regard to life expectancy, percutaneous coronary inter- vention does not produce survival benefit in patients with stable angina. By contrast, studies more than 40 years ago showed that cor- onary artery bypass grafting produced small gains in life expectancy in some patients. With current management strategies, patients with angina are living longer, but a few remain symptomatic with poor quality of life despite optimal medical treatment and having exhausted revascularization options. Psychological support is important to treat anxiety and depression and improve confidence, but other treatment options such as neuromodulatory techniques are not evidence- based and do not have guideline recommendations. Introduction Angina—the pain provoked by myocardial ischaemia—is usually caused by obstructive coronary artery disease that is sufficiently severe to restrict oxygen delivery to the cardiac myocytes (Box 16.13.3.1). It is one of the most common initial manifestations of coronary artery disease and occurs with almost equal frequency in women and men. Recent UK data indicate that, like other manifestations of coronary artery disease, the incidence of angina is declining. When angina occurs in patients without coronary artery disease it may be attributable to other ischaemic mechanisms such as se- vere anaemia resulting in inadequate oxygen delivery to the cardiac myocytes, or left ventricular hypertrophy secondary to hypertension or aortic stenosis

resulting in increased oxygen demand. The appro- priately named syndrome X is a diagnosis of exclusion in patients with angina for which there is no clear cause despite full cardiac investigation: their coronary arteries are not obstructed; abnormal microvascular function is one proposed mechanism. Syndrome X

16.13.3 Management of stable angina 3617 is more common in women than in men, and symptoms are often resistant to treatment. Prognosis is usually good although some studies have shown a small increase in the risk of myocardial infarc- tion and death. In most patients with angina caused by coronary artery dis- ease, quality of life is impaired in direct proportion to the severity of symptoms (Fig. 16.13.3.1). Prognosis is often good, particularly in patients with chronic stable symptoms receiving contemporary secondary prevention therapy, but in those with recently diagnosed angina risk is greater, with a 2 to 3% incidence of death or nonfatal myocardial infarction in the first year. Recognition of the need for early investigation has led to the widespread implementation of chest pain clinics in the United Kingdom and elsewhere to provide patients with suspected angina prompt treatment to relieve symp- toms and reduce risk. Referral for specialist assessment Referral for specialist assessment (Box 16.13.3.2) is indicated in all patients with known coronary artery disease—particularly those with previous myocardial infarction or coronary revascularization— who experience abrupt worsening of symptoms, often indicating plaque rupture and risk of impending infarction. However, referral decisions may be more difficult in patients presenting for the first time with chest pain. A noncardiac diagnosis accounts for most cases, but it is the task of the primary care or general physician to ensure that all those with suspected angina receive specialist as- sessment for confirmation of the diagnosis and risk stratification to identify those at greatest risk who need more intensive treatment. As in any screening process, false-negative diagnoses in which patients receive inappropriate reassurance must be avoided. By contrast, a proportion of false-positive diagnoses and referrals is acceptable, and among patients referred from primary care to chest pain clinics 75% have a noncardiac diagnosis. In primary care, the diagnosis of angina is based largely on the character of the symptoms and the age and sex of the patient, other risk factors further helping to identify those with a high prob- ability of coronary artery disease (see next). Access to noninvasive diagnostic tests can be helpful in primary care or the nonspecialist clinic, but there is often insufficient recognition of their limita- tions: the exercise ECG (for example) has a diagnostic sensitivity of only about 68%, which means that up to one-third of all cases with coronary disease are missed. For this reason, the clinical history remains the most useful basis for diagnosis and referral decisions. Thresholds for referral should be lowered in high-risk patients, including those with previous myocardial infarction and diabetes, and also in airline pilots and public service drivers whose occupa- tions might put others at risk in the event of myocardial infarction or sudden death. The recommendation that all patients with suspected angina be referred for specialist assessment leaves little room for prevarica- tion. Yet studies repeatedly show inequitable management of pa- tients with chest pain, those with the greatest need often being the very patients who receive the least intensive treatment. Thus, elderly patients with chest pain are at heightened risk, but are less likely than their younger counterparts to receive referral to chest pain clinics. Women are also disadvantaged and are less likely than men to be referred, even though it is increasingly recognized that angina in women is almost as common as in men and prognosis little better (Fig. 16.13.3.2). The reasons for this inequity are com- plex and poorly understood, but the consequences for healthcare are important. Box 16.13.3.1 Causes of angina Reduced myocardial oxygen supply • Coronary artery disease — Atherosclerosis — Spasm — Vasculitic disorders — Post radiation therapy • Severe anaemia

Increased myocardial oxygen demand • Left ventricular hypertrophy — Hypertension — Aortic stenosis — Aortic regurgitation — Hypertrophic cardiomyopathy • Right ventricular hypertrophy — Pulmonary hypertension — Pulmonary stenosis • Rapid tachyarrhythmias Indeterminate mechanism • Syndrome X baseline 2 years expected % of life aspects affected Angina grade 0 0 10 20 30 40 50 60 1 2 3 4 3–4 Fig. 16.13.3.1 Effect of angina on quality of life. Data are at baseline and 2 years after randomization in the Randomized Intervention Treatment of Angina (RITA) trial, showing impact of angina on life aspects encoded in part 2 of the Nottingham Health Profile. Note how quality of life deteriorates rapidly with worsening angina. Reprinted from Pocock SJ, Henderson RA, Seed P, Treasure T, Hampton JR (1996). Quality of life, employment status, and anginal symptoms after coronary angioplasty or bypass surgery. 3-year follow-up in the Randomized Intervention Treatment of Angina (RITA) Trial. Circulation, 94(2), 135–42. Box 16.13.3.2 Angina—indications for specialist cardiological referral • New-onset angina • Exclusion of angina in high-risk individuals with atypical symptoms • Worsening angina in a patient with previously stable symptoms • New or recurrent angina in a patient with history of: — Myocardial infarction — Coronary revascularization • Assessment of occupational fitness (e.g. airline pilots)

section 16 Cardiovascular disorders 3618 Clinical evaluation Angina varies considerably in its clinical presentation and its overlap with other entities can make the differential diagnosis of stable chest pain difficult. In most patients it is a manifestation of coronary ar- tery disease and the diagnostic challenge, therefore, is to determine whether the patient with chest pain has flow-limiting coronary ob- structions. A detailed description of the symptom complex is the most important step in the diagnostic process and in the context of other factors, particularly age, sex, and coronary risk factors, allows the clinician to estimate the likelihood of coronary artery disease. The extent of work-up required to exclude a noncardiac cause needs to be individually determined. The diagnosis is informed by the clinician’s intuition, experience, and interviewing skills, supported by investiga- tions such as the resting ECG and other noninvasive tests. A careful history provides the most useful diagnostic informa- tion, with three key characteristics defining anginal chest discom- fort (Fig. 16.13.3.3). Character—angina is experienced as a constricting discomfort across the front of the chest, often radiating to arms, throat, or jaw and lasting 5–15 minutes. Provocation—angina is nearly always provoked by exertion and sometimes by emotional stress. Relief—angina is relieved promptly by rest or short-acting nitrates. The presence of all three characteristics describes ‘typical angina’ while the presence of any two describes ‘atypical angina’. In patients with just one or none of these key characteristics, chest pain should be described as ‘nonanginal’. Angina is often worse in the morning, shortly after getting up, probably because catecholamine levels and blood pressure peak at this time of day. For similar reasons angina tends to be worse in cold weather and also after a heavy meal. In addition to typ- icality of symptoms and age and sex diagnosis is also influenced by a family history of premature coronary artery disease and by other risk factors—particularly diabetes, smoking, hypertension, dyslipidaemia, and advanced chronic kidney disease. Despite the reliance on clinical history in making a diagnosis of angina, it can be misleading, with atypical features, such as exertional dyspnoea in the absence of chest pain. Atypical presentations are said to be more common in patients with diabetes but, contrary to popular belief, there is little evidence that this also applies in women and South Asian people. The physical examination is often normal in the patient with an- gina but may contribute to diagnosis if signs of major risk factors are identified, particularly hypertension, cutaneous manifestations of dyslipidaemia, and complications of diabetes such as retinopathy and neuropathy. Patients with signs of peripheral vascular disease (e.g. absent pulses, arterial bruits)

have associated coronary involve- ment in most cases. Nitrate prescription angina (n>90 000) Test positive angina (n>27 000) Coronary mortality compared with sex-specific general population Lower 0.5 CI indicates confidence interval. 1.0 Coronary SMR 10 Higher Women Men Age group, y Sex 45–54 Women

Men 55–64 Women

Men 65–74 Women

Men 75–84 Women

Men 85–89 Women

Men 45–54 Women

Men 55–64 Women

Men 65–74 Women

Men 75–84 Women

Men 85–89 Women

Men Fig. 16.13.3.2 Prognosis of angina in women and men. Primary care electronic records for Finland linked with mortality data have permitted estimation of the prognosis of angina for men and women, presented here as standardized mortality ratios. Two mutually exclusive case definitions of angina were used based on nitrate prescription and test positivity, yielding over 90 000 and more than 27 000 cases, respectively. The data show that the contemporary prognosis of angina is not always good and at all ages is similar for men and for women. SMR, standardized mortality ratio. Reprinted from Hemingway H, McCallum A, Shipley M, Manderbacks K, Martikainen P, Keskimaki I (2006). Incidence and prognostic implications of stable angina pectoris among women and men. JAMA, 295, 1404–11.

16.13.3 Management of stable angina 3619 Simple laboratory investigations may also contribute to diagnosis by identifying groups at heightened risk of coronary disease due to renal dysfunction, dyslipidaemia, or diabetes. Anaemia is also im- portant to document because it may cause or—more commonly— exacerbate myocardial ischaemia. Noninvasive investigation Noninvasive testing is used primarily for diagnosis of coronary ar- tery disease, but also has a role in risk assessment (see next). By trad- ition, nearly all patients presenting with chest pain have an ECG, although it is of limited diagnostic value. Many patients with angina have a normal recording, although pathological Q waves reflecting previous myocardial infarction and regional ST-segment or T-wave changes show variable association with coronary disease. Other features of the ECG of potential relevance include tachycardia— particularly in patients with atrial fibrillation—and evidence of left ventricular hypertrophy, either of which may cause or exacerbate myocardial ischaemia. Indications for noninvasive testing, based on Bayesian principles, are guided by the level of diagnostic uncertainty following the clin- ical assessment. A 25-year-old with transient stabbing pains in the left side of the chest unrelated to exertion, for example, has non- anginal

symptoms and a positive noninvasive test would not modify that diagnostic judgement. All noninvasive tests may provide false- positive results with little incremental diagnostic value when the probability of coronary disease based on clinical assessment is very low. It is partly for this reason that contemporary NICE guidelines recommend no diagnostic testing in patients with nonanginal chest pain, unless the ECG shows changes suggestive of underlying cor- onary artery disease such as pathological Q waves or ischaemic ST- segment or T-wave changes. By contrast, diagnostic uncertainty is greater in patients with typical or atypical chest pain, contemporary diagnostic models predicting an intermediate probability of coronary artery disease between 10% and 90%, regardless of age and gender. Guidelines therefore recommend noninvasive testing because the results, positive or negative, can help resolve diagnostic uncertainty and contribute to appropriate further management. The choice of noninvasive test has been the subject of much recent debate, with US guidelines favouring the exercise ECG and 'func- tional' imaging tests, while the UK's 2016 NICE guideline update, based on cost-effectiveness analysis, favours 'anatomical' imaging by computed tomography coronary angiography (CTCA) (Fig. 16.13.3.4). The European guideline also favours CTCA if the pretest probability of disease is low (<50%), but functional imaging tests are preferred if the probability is higher. The exercise ECG and functional imaging tests all seek to deter- mine if regional myocardial ischaemia can be induced by exertional or pharmacological (e.g. dobutamine) stress (Fig. 16.13.3.5). Induction of ischaemic changes is considered to be diagnostic of ob- structive coronary artery disease. Anatomical testing by CTCA, on the other hand, provides angiographic images of the coronary cir- culation and direct evidence of obstructive disease. The diagnostic value of CTCA tends to be higher than functional imaging tests, with sensitivity and specificity greater than 90% in most studies. Nevertheless, it should be recognized that none of noninvasive tests used in the diagnosis of angina is perfect, with all variably prone Take a history Physical examination (Routine investigation) • Identify risk factors for CVD • Identify signs of other CVD • Identify noncoronary causes of angina (eg severe aortic stenosis) • Exclude other causes of chest pain • Blood tests to rule-out conditions exacerbating anfina eg anaemia • Associated symptoms • Characteristics of chest pain • Age and sex • Cardiovascular history – – – • Cardiovascular risk factors • 12-lead ECG–changes consistent with coronary disease – Pathological Q waves – Left bundle branch block – Regional ST/T change Clinical diagnosis driven mainly by the characteristics of chest pain Central, lasting about 5–15 minutes Provoked by exertion or emotional stress Relieved promptly by rest or nitrtates NONANGINAL PAIN ≤1 characteristic ATYPICAL ANGINA 2 characteristics TYPICAL ANGINA all 3 characteristics
Fig. 16.13.3.3 Clinical diagnosis of angina. Reproduced from Heart, Timmis A, Roobottom CA, vol. 103, pp. 982–6, copyright 2017, with permission from BMJ Publishing Group Ltd.

section 16 Cardiovascular disorders 3620 to delivery of false-positive or false-negative results. Partly for this reason, underdiagnosis of angina is quite common, and patients in chest pain clinics reassured with a diagnosis of noncardiac chest pain account for up to one-third of myocardial infarctions and coronary deaths during the next 5 years. Overdiagnosis is also common, as re- flected in the large and increasing proportion of patients with chest pain referred for cardiac catheterization and found to have unob- structed coronary arteries. Exercise ECG Once widely used for diagnosis of coronary artery disease, ex- ercise ECG testing is now giving way to the newer generation of noninvasive diagnostic tests described next. Details are described in Chapter 16.3.1. The sensitivity and specificity of the exercise ECG is 68% and 77%, respectively, with diagnostic value tending to be lower in women than in men. The regional development of planar or down- sloping ST-segment depression, with gradual recovery when exercise stops, is usually diagnostic

when associated with typical chest pain. The exercise ECG may also provide prognostic information: low exercise tolerance, ST depression early during exercise, an exertional fall in blood pressure, or exercise-induced ventricular arrhythmias all point to an increased risk of myocardial infarction or sudden death. The Duke treadmill score, which takes into account dur- ation of exercise, degree of ST-segment deviation, and angina pro- vides a quantitative prognostic assessment and has proved useful for determining the urgency of coronary arteriography. Isotope perfusion imaging This is also widely used for diagnostic purposes and, although more costly and time-consuming than the exercise ECG, has enhanced diagnostic accuracy (sensitivity 80–90%, specificity about 80%). Details are described in Chapter 16.3.3. Fixed defects, present at rest and during stress, indicate areas of myocardial infarction, but re- versible defects are indicative of ischaemia in patients with angina. Isotope perfusion imaging also provides useful prognostic in- formation, the extent and severity of perfusion defects (fixed or re- versible), the degree of lung uptake of radioisotope (reflecting level of pulmonary capillary pressure), and the calculated ventricular volume and ejection fraction all predicting risk of future events. Cardiac magnetic resonance (CMR) perfusion imaging This has an important role in the investigation of patients with sus- pected angina. First-pass perfusion imaging with gadolinium offers high levels of diagnostic accuracy (sensitivity c.90%, specificity Central chest discomfort lasting 5–15 minutes Provoked by exertion or emotional stress Relieved by rest or nitrates No diagnostic testing Diagnostic testing • ≥64-slice CTCA for all patients • Functional imaging if CTCA is non- diagnostic Typica anginal All 3 characteristics A typical angina 2 characteristics Pretest probability of obstructive coronary disease 10–90% refer directly for diagnostic testing Nonanginal pain ≤1 characteristics Clinical assessment Fig. 16.13.3.4 NICE guideline (2016 update) for investigation of chest pain. Angina Ischaemic ST depression Global LV dysfunction Regional systolic dysfunction Regional diastolic dysfunction Perfusion abnormality Normal LV function Perfusion imaging LV wall motion analysis Increasing myocardial oxygen demand Electrocardiography Clinical assessment Increasing exercise
Fig. 16.13.3.5 Diagnosis of angina: functional testing for coronary artery disease. Functional tests are designed to identify evidence of regional ischaemia induced by exercise or drugs. Abnormalities of perfusion, left ventricular (LV) wall motion or electrical repolarization can all be detected by imaging or ECG monitoring. Ischaemia may also cause angina, emphasizing the importance of the clinical history in the diagnostic process.

 80%) for detection of myocardial ischaemia. Although unable to provide the same coronary anatomical definition as CT or conven- tional angiography, it also provides additional prognostic informa- tion about ventricular volumes, ejection fraction, and the extent of myocardial infarction, which combine to predict risk of future events. The identification of viable and hibernating myocardium with CMR may be used to guide revascularization strategies. Stress echocardiography This is used increasingly for diagnostic purposes in patients with suspected angina, but is more dependent than other noninvasive tests on the technical and interpretive skills of the operator. Details are described in Chapter 16.3.2. In expert hands the sensitivity and specificity are around 80% for diagnosing coronary artery disease in patients with suspected angina. Left ventricular imaging during dobutamine infusion permits assessment of regional wall motion in response to adrenergic stress, with decreasing systolic wall motion or wall thickening indicating ischaemia and the likelihood of cor- onary artery disease. CT coronary angiography (CTCA) This is emerging as the noninvasive imaging test of choice for many patients with suspected angina (Fig. 16.13.3.6). Modern scanners provide high quality angiographic images of the epicardial cor- onary arteries, with diagnostic sensitivity of around 95% reflecting the

very low rate of false-negative findings. This makes CTCA ideal for ruling out coronary artery disease, current European guidelines recommending its application in all patients with a probability of coronary artery disease between 10% and 50%. Specificity is also high compared with other imaging modalities, and based on a cost- effectiveness analysis the NICE guideline now recommends CTCA as the noninvasive imaging test of choice for patients with typical or atypical angina. All such patients have an intermediate probability of coronary artery disease between 10% and 90% according to con- temporary diagnostic models and stand to benefit from noninvasive testing to resolve diagnostic uncertainty. The effectiveness of CTCA for identifying patients with obstructive coronary artery disease is confirmed by the enhanced diagnostic yield of invasive coronary arteriography in patients selected by prior CTCA instead of other noninvasive diagnostic tests. CT imaging also provides information about the arterial wall, particularly the severity and distribution of coronary cal- cification which relates to the severity of coronary atheroscler- osis. Nevertheless, some cautions about the clinical application of CTCA need to be acknowledged. Image quality and image in- terpretation may be adversely affected by obesity, high coronary calcium burden, cardiac arrhythmias, and tachycardia, although improvements in scanner technology have helped mitigate these factors (see Chapter 16.3.3) Risk assessment of angina Recent clinical trials of patients with chronic angina show that ag- gressive treatment under cardiological supervision reduces risk considerably such that long-term prognosis is good, with all-cause mortality rates of about 1.5% per year. However, prognosis is worse in cohorts attending chest pain clinics in the early weeks or months after symptom onset, with mortality rates in excess of 3% in the first year. Identification of high-risk patients is therefore an important part of the initial assessment to inform decisions about the urgency and aggressiveness of treatment in individual cases. Clinical indicators of risk As with diagnosis, it is the clinical assessment that provides the most useful prognostic information in angina. Risk is greatest in patients who are old, those with typical symptoms and—contrary to con- ventional wisdom—those with more severe symptoms. Women and South Asians with angina do not appear to be at greater risk. Risk increases with the number of ‘reversible’ risk factors, particularly diabetes, smoking, hypertension, and dyslipidaemia, all of which are important targets for treatment. Risk is also increased in patients with a history of myocardial infarction or stroke. Tachycardia is associated with increased risk, although treatment to slow the heart rate is directed primarily at preventing exertional ischaemia. Heart failure increases risk substantially. The most useful laboratory markers of risk are blood concentrations of lipids (particularly low- density lipoprotein (LDL) cholesterol and apolipoproteins), glycated haemoglobin, and creatinine. Cardiac troponin concentration, widely used for diagnosis of myocardial infarction, has more re- cently been identified as an independent predictor of risk in angina. Noninvasive testing for risk assessment Generally speaking, negative test results indicate a good prognosis and a low level of urgency for further invasive investigation. However, when test results suggest severe and extensive ischaemia, risk is often high with important implications for future management. Risk scores Many scores have been developed for determining cardiovascular risk in healthy populations and in patients with acute myocardial infarction. Scores are also available for risk assessment in patients with suspected angina and in patients with an established diagnosis of chronic stable angina, based on many of the clinical and laboratory Fig. 16.13.3.6 Noninvasive coronary angiography by MDCT (multidetector CT). The right coronary artery (arrowed) is patent but has localized areas of dense calcification in its proximal and mid segments denoting atherosclerosis.

section 16 Cardiovascular disorders 3622 variables described here, plus echocardiographic measurement of left ventricular function. As yet, angina risk scores have not found major application in clinical practice. Invasive testing for risk assessment In patients with angina, risk of myocardial infarction and cardio- vascular death is related to the extent and severity of angiographic coronary artery disease. Risk is particularly high when obstructive disease (luminal stenosis >50%) affects all three of the major cor- onary arteries. In patients with left main coronary artery disease, death is inevitable in the event of left main occlusion and urgent revascularization is usually recommended. Novel biomarkers A range of inflammatory markers, including C-reactive protein, have been assessed in stable patients with coronary artery disease, but their incremental predictive value for future coronary events is very low once conventional risk factors have been taken into account. Brain natriuretic peptide may be more useful in this group of patients, although currently its main clinical application is in the diagnosis of heart failure. Circulating concentrations of troponin I or T measured with high sensitivity assays have also been shown to identify high-risk subgroups in patients with stable angina. Treatment of angina The purpose of treatment is to correct symptoms and reduce risk, thereby improving both the quality of life and its duration (Fig. 16.13.3.7). General measures Comorbidities that exacerbate angina include anaemia, obesity, and thyrotoxicosis, all of which need treating. Most important, how- ever, is hypertension, which increases myocardial oxygen demand in proportion to its severity. Simple lowering of blood pressure will often correct angina without the need for additional symptomatic treatment. Atrial fibrillation is also important because it is common, particularly in elderly patients, and increases myocardial oxygen de- mand due to tachycardia. Symptom relief can often be achieved by heart rate control or cardioversion. Aortic stenosis is another cause of angina that can be corrected by valve replacement. Secondary prevention The risk of myocardial infarction, stroke, and cardiovascular death can be reduced by lifestyle modification and specific drug therapy. Logic also requires that major atherogenic risk factors—particularly diabetes, smoking, hypertension, and dyslipidaemia—are treated vig- orously in patients with angina, evidence for risk reduction being best for blood pressure control, smoking cessation, and LDL cholesterol reduction. Strict glycaemic control in type 2 diabetes, provides some protection against ischaemic end-points and the recently introduced sodium glucose co-transporter (SGLT-2) inhibitors and glucagon-like peptide (GLP-1) agonists seem particularly promising in this respect. Lifestyle modification Evidence-based recommendations are for smoking cessation, ex- ercise training, and a Mediterranean-style diet characterized by low intake of total and saturated fats and increased intake of fresh fruits and vegetables, and cereals rich in fibre, antioxidants, min- erals, vegetable proteins, and B-group vitamins. Weight reduction in Fig. 16.13.3.7 Management of angina (NICE 2011).

 obese patients is also recommended, particularly those with hyper- tension, dyslipidaemia, or diabetes. Secondary prevention drugs All patients with angina should receive aspirin 75–150 mg daily, its antiplatelet activity reducing the thrombotic response to plaque rupture and protecting against myocardial infarction and stroke. Patients intolerant of aspirin despite proton pump inhibition should be treated with a P2Y12 receptor antagonist (clopidogrel, prasugrel or ticagrelor) which offer equivalent protection. Patients with angina should also receive statin therapy to lower LDL cholesterol, thereby reducing lipid accumulation in the arterial wall and stabilizing the atherosclerotic plaque against rupture. The NICE guideline recommendation is for high intensity statin treat- ment with atorvastatin 80 mg daily with a view to reducing LDL cholesterol by at least 40%. European guidelines recommend treat- ment to an LDL target of 1.8 mmol/litre. Failure to respond ad- equately to statins provides

indication for the addition of ezetimibe to further lower LDL by reducing cholesterol absorption from the bowel. In those patients diagnosed with familial hypercholesterol- aemia, lipid PCSK9 inhibitors now have an indication for producing yet greater LDL reductions. The cardiovascular risk associated with low high-density lipoprotein (HDL) is well established, but treat- ment to increase HDL with nicotinic acid derivatives does nothing to reduce risk in patients with coronary artery disease. The more potent cholesteryl ester transfer protein inhibitors have also proved ineffective and their development has been largely abandoned. Angiotensin-converting enzyme (ACE) inhibition provides some additional protection against cardiovascular endpoints in patients with angina, but this probably relates to their blood pressure lowering effect and current recommendations are for their use only in patients with angina who have additional indications for ACE inhibition such as hypertension, heart failure, or diabetes. β-Blockers, though widely used for symptomatic treatment, have no clear evidence-based indication for secondary prevention in patients with angina unless there is associated left ventricular dys- function, when prognostic benefit is well established. Antioxidant vitamins C and E and omega-3 fatty acids have failed the test of clinical trials for secondary prevention in coronary artery disease. Similarly, there appears to be no role for hormone replacement therapy for protecting against coronary events in postmenopausal women. Antianginal drugs Drugs used to treat angina reduce ischaemia by improving the balance between myocardial oxygen supply and demand (Fig. 16.13.3.8). Guideline recommendations are that medical therapy with antianginal drugs should be tried before angioplasty or surgery is considered, except in those patients with stable angina with left main stem or multivessel coronary disease in whom there is evidence that surgical revascularization might improve prognosis. The antianginal drugs recommended for initial treatment are a β-blocker and a calcium channel blocker, together with a short- acting nitrate for prompt alleviation of angina attacks. If these drugs are not tolerated or are contraindicated, alternative antianginals listed next may be introduced, but if angina remains troublesome despite treatment with a β-blocker and calcium channel blocker, revascularization requires consideration—not the addition of fur- ther antianginal drugs. β-blockers These drugs reduce myocardial oxygen demand, principally by slowing the heart rate, although reductions in left ventricular wall tension (blood pressure) and contractility also contribute. Resting heart rate should not be allowed to drop below 55 beats per minute. Choice of β-blocker is largely determined by patient acceptability, with preference given to once-daily cardioselective agents such as bisoprolol. Effective relief of exertional angina can often be obtained without recourse to other drugs if the heart rate response to exercise can be reduced sufficiently. There is a clear indication for β-blockers when angina occurs in patients with heart failure or asymptomatic left ventricular dysfunction. They are usually well tolerated, but noncardiac side effects, particularly fatigue and erectile dysfunction, may be troublesome even with cardioselective agents. β-Blockers are contraindicated in patients with bronchial asthma. Calcium blockers Like nitrates, these are vasodilators and improve myocardial oxygen balance by their effect on coronary flow and peripheral resistance. Angina complicated by hypertension provides a clear indication for drugs of this class, and amlodipine is usually the pre- ferred agent. Diltiazem and verapamil are also useful because, in addition to vasodilator activity, they often produce minor reduc- tions in heart rate, although combination therapy with β-blockers is best avoided. Nifedipine, which tends to increase heart rate, is not recommended for treatment of angina. Side effects of calcium blockers are related to vasodilatation and include facial flushing, postural dizziness, and ankle oedema. Nitrates These drugs improve myocardial oxygen delivery and reduce demand by direct coronary and peripheral vascular dilatation. Sublingual glyceryl trinitrate by tablet or spray should be given to all patients with angina, rapid absorption through the buccal mucosa providing

symptomatic relief within 3 min. It can also be used prophylactically to prevent angina during exertion. Long- acting isosorbide mononitrate for regular oral administration is widely used, although variable tolerance to its therapeutic action Increased O2 delivery Coronary flow

• Nitrates

• Calcium blockers

• Nicorandil

• Revascularization

(CABG, PCI) Reduced O2 demand Heart rate

• β-blocker

• Ivabradine LV wall tension

• β-blocker

• Nitrates

• Nicorandil

• Calcium blockers

• Ranolazine Contractility

• β-blocker

• Calcium blockers Modify energy metabolism

• Trimetazidine O2 delivery O2 demand Angina occurs if demand exceeds supply Fig. 16.13.3.8 Symptom relief with drugs.

section 16 Cardiovascular disorders 3624 may occur. Side effects are rarely troublesome apart from headache during the first few days of treatment. Potassium channel openers Nicorandil is the only drug in this group licensed to treat angina. It is a vasodilator with effects comparable to those of long-acting ni- trates. The principal side effect is headache. Less common but more serious are gastrointestinal ulcers that will not heal unless nicorandil is withdrawn. Trimetazidine This interesting compound is licensed for treatment of angina in a number of European countries (not the United Kingdom). Its pharmacological effects are metabolic, not haemodynamic, with coupling between glycolysis and carbohydrate oxygenation re- stored by shifting cardiac energy metabolism from oxygenation of fatty acids (the preferred myocardial substrate) to glucose, thus preserving intracellular ATP levels. Antianginal effects are compar- able to other agents. Side effects, including gastrointestinal disturb- ance, are rarely troublesome. Ivabradine Ivabradine inhibits the If channel in the sinus node, reducing the slope of diastolic depolarization and slowing the heart rate. The ef-

fect of ivabradine on heart rate is comparable to that of β-blockers, but it is only effective in patients with normal sinus rhythm (rate reduction does not occur in atrial fibrillation). Based on the results of a recent trial, however, the indication for ivabradine is restricted to patients with continuing symptoms in whom β-blockers fail to reduce the heart rate below 70 beats per minute. In such patients the addition of ivabradine may be helpful but heart rate should not be allowed to fall excessively. There is an additional indication for ivabradine in patients who have a contraindication to or intoler- ance of β-blockers and in whom calcium channel blockers such as amlodipine have failed to control symptoms. Ivabradine is gener- ally well tolerated and mild visual side effects tend to resolve during treatment. Ranolazine Ranolazine's mechanism of action appears to involve inhibition of the late inward sodium channel which indirectly prevents calcium overload of ischaemic myocytes and reduces diastolic wall tension and oxygen demand. Heart rate or blood pressure are unaffected. Antianginal effects are additive to those of β-blockers and calcium blockers. Side effects including constipation and dizziness are rarely troublesome. Revascularization In the patient with angina, revascularization provides a non- pharmacological means of improving myocardial oxygen delivery by restoring coronary flow to the ischaemic myocardium. More than 60% of all revascularization procedures in stable angina are now by percutaneous intervention using balloon angioplasty and stenting (Fig. 16.13.3.9). The remainder are by coronary artery by- pass surgery (CABG), the choice depending largely on the extent and severity of coronary artery disease. At present, this can only be determined by coronary angiography which is an essential pre- requisite of revascularization in the management of angina. See Chapters 16.3.4 and 16.13.5 for further discussion. Which patients with stable angina should undergo
coronary angiography? Guideline recommendations are for angiography in patients with continuing moderate or severe angina despite optimal medical treat- ment comprising antianginal drugs (typically a β-blocker and cal- cium channel blocker plus short-acting nitrates), aspirin, and statins. Other groups for whom angiography is recommended include those who have been successfully resuscitated from sudden cardiac death (a) (b) Fig. 16.13.3.9 Coronary revascularization by PCI. Right coronary arteriogram (a) before stenting and (b) after deployment of a drug-eluting stent across the diseased segment (arrowed) in the proximal part of the vessel. The patient had stable angina and experienced complete relief of symptoms after the procedure.

 or who have life-threatening ventricular arrhythmias and those with suspected or known coronary artery disease whose jobs (e.g. piloting aircraft, driving public service vehicles) are dependent on a normal or fully revascularized coronary circulation. It may also be indicated in patients unwilling or unable to take antianginal drugs, or those in whom there is important diagnostic uncertainty despite noninvasive investigation. In patients whose angina has responded satisfactorily to medical treatment there is no absolute requirement for angiog- raphy but the potential for small gains in life expectancy with CABG for high-risk coronary anatomy (left main or three-vessel disease) should be discussed, and angiography offered to those who wish to have the coronary anatomy defined. Choice of revascularization procedure—CABG vs. PCI In symptomatic patients who have undergone cardiac catheter- ization, revascularization is generally indicated if one or more of the major coronary arteries—or their large branches—have flow- limiting stenoses (>70% luminal narrowing) or occlusions. The choice of revascularization procedure is dependent on a range of factors and should be discussed in a multidisciplinary group that includes cardiologists and cardiac surgeons: • Coronary anatomy—historically, PCI has been preferred for single-vessel and two-vessel coronary artery disease and CABG for more extensive disease. This preference, based largely on presumed

prognostic benefit for CABG in patients with three- vessel or left main stem disease (see next), has now given way to procedure selection based on coronary scoring systems. Most widely used is the SYNTAX score designed to quantify the com- plexity of left main or three-vessel disease according to simple lesion criteria readily accessible from the coronary arteriogram. If the SYNTAX score is less than 22, signifying low lesion com- plexity, 5-year outcomes favour revascularization by PCI, re- gardless of the number of diseased vessels. If the SYNTAX score is higher CABG should also be considered, and for scores more than 33 (signifying severe lesion complexity) CABG produces unequivocally better 5-year outcomes than PCI. In making revascularization decisions, however, other factors are also im- portant, and there is now clear evidence favouring CABG for patients with diabetes and multivessel disease. • Patient preference—PCI is often preferred because it avoids sur- gery, requires no more than 48 h hospitalization (day-case PCI is now feasible), and permits early return to normal activities within a few days of the procedure. In expressing a preference, however, it is important that the patient is properly informed of the relative risks and benefits of PCI and CABG in his or her particular case. • Procedural risk—mortality is lower for PCI than CABG (0.9% vs. 2.2%). Stroke risk may also lower, but rates of nonfatal myocardial infarction are comparable. • Symptomatic benefit—this is comparable for PCI and CABG, but recurrence of symptoms and need for repeat revascularization is higher for PCI because of coronary restenosis in the months following a successful procedure. Indeed, restenosis has been the Achilles heel of PCI, and until the introduction of coronary stents affected 30% or more of all patients. Since then stenting has become widespread, producing more effective coronary pa- tency although reductions in rates of restenosis to less than 10% had to await the introduction of drug-eluting stents that deliver antiproliferative drugs (e.g. sirolimus, paclitaxel) locally within the coronary artery. The prospect of providing long-term relief of symptoms without the need for repeat procedures has consider- ably enhanced the clinical value of PCI. • Prognostic benefit—There have been no studies showing survival benefit for PCI in patients with stable angina. For CABG, the small gains in life expectancy that have been reported in patients with left main stem coronary disease and three-vessel disease are from studies nearly 40 years ago and their contemporary relevance may have changed with advances both in surgical techniques and in medical therapy. Indeed, it is generally accepted that improvements in the prognosis of coronary artery disease in the last 25 years have little to do with revascularization, but much to do with lifestyle changes and advances in secondary prevention therapy. Refractory angina With current management strategies patients with angina are living longer, but some (perhaps 5 to 10%) remain symptomatic on optimal medical treatment, having exhausted revascularization options. These patients commonly have extensively collateralized coronary circulations and well-preserved left ventricular function such that prognosis is not worse than other patients with angina, but quality of life is poor because of refractory symptoms. Psychological support is important to treat anxiety and depression and improve confidence. Other options for further antianginal therapy are not evidence- based and are not recommended in international guidelines. These include neuromodulatory techniques (stellate ganglion block, trans- cutaneous electrical nerve stimulation, spinal cord stimulation) and enhanced counterpulsation therapy using pressure cuffs applied to the lower limbs that are inflated sequentially during diastole. FURTHER READING Boden WE, et al. (2007). Optimal medical therapy with or without PCI in stable coronary disease. N Engl J Med, 35, 1503–16. Doris MK, Newby DE (2016). How should CT coronary angiography be integrated into the management of patients with chest pain and how does this affect outcomes? Eur Heart J Qual Care Clin Outcomes, 2, 72–80. Fihn SD, et al. (2012). ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on

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