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16.5.3 Chronic heart failure 3407 Costanzo MR, et al. (2017). Extracorporeal ultrafiltration for fluid overload in heart failure: current status and prospects for further research. J Am Coll Cardiol, 69, 2428–45. Gray A, et al. 3CPO Trialists (2008). Noninvasive ventilation in acute cardiogenic pulmonary edema. N Engl J Med, 359, 142–51. Harris P (1983). Evolution and the cardiac patient. Cardiovasc Res, 17, 313–19, 373–8, 437–45. MacIver DH, Clark AL (2015). The vital role of the right ventricle in the pathogenesis of acute pulmonary edema. Am J Cardiol, 115, 992–1000. MacIver DH, Dayer MJ, Harrison AJ (2013). A general theory of acute and chronic heart failure. Int J Cardiol, 165, 25–34. National Institute for Health and Care Excellence (2014). Acute heart failure: diagnosis and management. Clinical guideline. https://nice. org.uk/guidance/cg187 Ponikowski P, et al. (2016). 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J, 37, 2129–200. Tharmaratnam D, Nolan J, Jain A (2013). Management of cardiogenic shock complicating acute coronary syndromes. Heart, 99, 1614–23. Thiele H, et al. IABP-SHOCK II Trial Investigators (2012). Intraaortic balloon support for myocardial infarction with cardiogenic shock. N Engl J Med, 367, 1287–96. 16.5.3 Chronic heart failure: Definitions, investigation,

and management John G.F. Cleland and Andrew L. Clark ESSENTIALS Heart failure is a common clinical syndrome, predominantly a disease of older people, often presenting with breathlessness, fatigue, and per- ipheral oedema. Its pathophysiology is complex, with a common fea- ture being salt and water retention, possibly triggered by a relative fall in renal perfusion pressure. Common aetiologies include ischaemic heart disease, hypertension, and valvular heart disease. New treatments have improved prognosis substantially over the past two decades. Early diagnosis relies on a low threshold of suspicion and screening of people at risk. Low plasma concentrations of BNP/NT- proBNP exclude most forms of heart failure, and intermediate or high concentrations should prompt referral for echocardiography to identify possible causes and determine the left ventricular ejection fraction (LVEF), leading to classification as heart failure with reduced LVEF (<40%, HFrEF), normal LVEF (>50%, HFnEF), or borderline LVEF
(40–50%, HFbEF). HFbEF and HFnEF are managed similarly by cur- rent guidelines. Treatable causes for heart failure (e.g. valvular disease, tachyar rhythmias, thyrotoxicosis, anaemia, or hypertension) should be iden- tified and corrected. Pharmacological therapy is given to improve symptoms and prognosis. Diuretic therapy is the mainstay for control of congestion and symptoms, but its effect on long-term prognosis is un- known. For patients with HFrEF, either angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or angiotensin receptor– neprilysin inhibitors, combined with β-blockers and mineralocor- ticoid receptor antagonists (triple therapy) provide both symptomatic and prognostic benefit. Other treatments that may be appropriate in particular cases include ivabradine, digoxin, cardiac resynchronization therapy, and implantable defibrillators. Heart transplantation or assist devices may be options for highly selected patients with end-stage heart failure; many others may benefit from palliative care services. Introduction Heart failure is the most common malignant disease in the United Kingdom. Heart failure in its various manifestations now causes or complicates twice as many hospital admissions (about half a million deaths and discharges each year in the United Kingdom) as do all cancers or acute coronary syndromes combined. This is likely to be a gross underestimate of total activity as the diagnosis of heart failure is often missed or ignored during admission. In the community, heart failure syndromes are almost as common as diabetes mellitus and far more deadly. For some cardiac phenotypes (e.g. left ventricular systolic dys- function), treatment is often highly effective and may even be cura- tive, but diagnostic awareness is low and care, when given, is often fragmented and disorganized. The reasons for the current clinical neglect of heart failure are not entirely clear but may reflect the lack of a robust definition, the difficulty and uncertainties of its clinical diagnosis, the relative complexity of its treatment, all combined with ageism and fatalism on the part of both the clinician and patient. Definition No consensus has been reached on a simple, practical universal definition of heart failure. Indeed, it may be better to consider the diagnosis of heart failure across a spectrum of certainty based on clinical acumen supported by blood tests (particularly natriuretic peptides) and cardiac imaging. Until now, most experts and guidelines have required that the pa- tient should have symptoms before a diagnostic label of heart failure is applied. Of course, a sedentary lifestyle and liberal use of diuretics may mask symptoms. Simply asking the patient to take a walk will often reveal how poor their effort tolerance is, and stopping diuretics will often lead to the diagnosis becoming obvious. Other specialties use biochemical definitions to define organ failure (kidney, pancreas, liver). Central to the concept of heart failure is congestion, indicating that the heart is unable to sustain a normal filling (atrial) pressure for the required cardiac output. Cardiac output is usually fairly normal at rest until the late stages of heart failure. How then should congestion be measured? Natriuretic pep- tides, hormones that are secreted by the stressed heart and designed to counter sodium retention, provide a simple objective method of detecting

congestion, even before it becomes clinically overt (Fig. 16.5.3.1). Thus, heart failure could be considered cardiac dys- function leading to an increase in natriuretic peptides. Natriuretic

section 16 Cardiovascular disorders 3408 peptides are now an essential tool for the early detection and con- firmation of a diagnosis of heart failure in any modern health service. Broadening the definition of heart failure has many consequences, the most obvious being a great increase in the number of patients. About 3% of the adult population is taking loop diuretics for no obvious reason other than symptoms or signs suggestive of heart failure. Currently, most cases of heart failure are diagnosed during a hospital admission, suggesting that the diagnosis is usually missed until the problem is bad enough to provoke severe symptoms. The onset of symptomatic heart failure may well be precipitated by an acute event, but usually on a back- ground of chronic cardiac dysfunction. Earlier diagnosis will increase identification in the community before the onset of severe symptoms and at a time when therapy might be more effective. Clinical physiology Heart failure can be considered as a sequence of unfortunate events (Fig. 16.5.3.2), starting with cardiac (usually left ventricular) dys- function leading to haemodynamic changes that are often initially subtle, including a rise in atrial pressures and a fall in blood pressure below the set-point for renal sodium retention. This triggers acti- vation of neuroendocrine systems such as the renin–angiotensin– aldosterone and sympathetic nervous system in an attempt to restore blood pressure by vasoconstriction and blood volume expansion. This has long-term deleterious effects on the heart. Fortunately, there is also activation of counter-regulatory mechanisms, most not- ably the natriuretic peptides, which attempt to prevent sodium re- tention and delay the onset of symptomatic congestion. Eventually, counterregulatory systems are overwhelmed, and clinical evidence of congestion appears, manifest either as breathlessness (loosely re- lated to left atrial pressure) or peripheral oedema (loosely related to right atrial pressure). The treatment of heart failure revolves around preventing or reversing congestion and avoiding sudden death due either to arrhythmias or vascular events, which can arise at any time. Cardiac (imaging) phenotypes Cardiac phenotype is strongly linked to the aetiology of cardiac dys- function and is a key determinant of management. For some cardiac phenotypes there is little evidence that treatment alters outcome. Fig. 16.5.3.1 Natriuretic peptides are the earliest and most sensitive sign of congestion but do not distinguish between cardiac and renal causes. Cardiac imaging is less sensitive and accurate (i.e. abnormal cardiac function may not cause congestion) for detecting congestion but, along with tests for heart rhythm and renal function, it helps to determine the cause of congestion. Symptoms and signs are late manifestations of congestion and usually only first detected when they have deteriorated sufficiently to precipitate a hospital admission. Left ventricular dysfunction Rise in left atrial pressure At rest During stress Volume (fluid load, exercise) • Pressure (hypertension, exercise) • • Pulmonary congestion • Breathlessness • Pulmonary arteriolar hypertrophy & vasoconstriction • Pulmonary hypertension • Rise in right atrial pressure • Peripheral oedema • Peripheral congestion • Tricuspid valve regurgitation • Right ventricular dysfunction • • Mitral regurgitation Fig. 16.5.3.2 Development and progression of heart failure.

16.5.3 Chronic heart failure 3409 Few patients have a single pure phenotype; most patients manifest several phenotypes, but usually one is dominant (Table 16.5.3.1). When heart failure is associated with a reduced left ventricular ejection fraction (LVEF) this is often termed HFrEF or left ven- tricular systolic dysfunction (LVSD). Patients with heart failure and a normal or preserved LVEF are termed HFnEF and HFpEF, respect- ively. Left ventricular diastolic dysfunction (LVDD) is a subset of HFnEF as it is possible to have HFnEF without LVDD (e.g. patients with isolated right

ventricular dysfunction). Various authorities suggest different LVEF thresholds for defining HFnEF, with the cut-off ranging from less than 40% to over 50%. Since echocardiographers usually refer to a LVEF of under 50% as LVSD the terminology is confusing, and some believe that patients with an LVEF of 40–50% should be considered a separate group HFbEF (heart failure with a borderline LVEF), which seems a helpful concept. LVEF measured by conventional echocardiography is only accurate to within about 10%, although more advanced imaging techniques such as cardiac MRI (CMRI) may have greater precision. Each of the phenotypes is heterogeneous, particularly HFnEF (Fig. 16.5.3.3). HFrEF is the predominant cardiac phenotype in men and patients aged less than 75 years and is often due to ischaemic heart disease. HFnEF is the predominant phenotype in older women and is often due to hypertension. In patients with HFrEF, it is im- portant to consider to what extent contractile dysfunction is due to dysfunction of viable myocardium, which may be reversible, or to consolidated scar that is likely to be irreversible using existing tech- nology. The relative contribution of extracellular matrix and fibrosis and impaired cardiac myocyte relaxation to HFnEF is uncertain, and the therapeutic target at the myocardial level is unclear. Heart failure due to valve disease may occur at any age, but degenerative valve disease is an increasingly common cause in older people. Risk factors and aetiology The most important risk factor for heart failure is age. It is likely that everyone will develop heart failure if they live long enough. Biological rather than chronological age may account for the link between physical frailty and the risk of developing heart failure. Currently, one in five people is expected to develop heart failure be- fore they die, which may be a gross underestimate given the diag- nostic gap outlined earlier. The most important medical risk factors for developing heart failure are hypertension and ischaemic heart disease, and their combination may confer more than additive risk (Table 16.5.3.1). Both may go undetected and untreated for years; the onset of symptoms of heart failure may be the first time the patient seeks help. There is a wealth of evidence that hypertension, even when detected, is often poorly man- aged. Alarmingly, studies suggest that most myocardial infarctions, perhaps especially among older people, do not provoke symptoms sufficient for the person to seek immediate medical assistance. Good treatment of hypertension and other risk factors for coronary artery disease will undoubtedly delay the onset of disease. Poor lifestyle and inferior medical care probably account for the association between social deprivation and the onset of heart failure at an earlier age. Among patients aged under 50 years, cardiomyopathies and con- genital heart disease account for a large proportion of heart failure. Table 16.5.3.1 Common cardiac phenotypes in heart failure HFrEF HFbEF HFpEF/HFnEF LVEF <40% 40–50%

> 50% Ischaemic heart disease XXX XX X Hypertension X XX XXX Atrial fibrillation XX XX XXX Dilated cardiomyopathy XXX ? NA Aortic stenosis X XX XXX Mitral regurgitation XX XX XX Number of crosses reflects strength of association (although not necessarily proportion affected or prevalence). HFrEF = heart failure with a reduced left ventricular ejection fraction. HFbEF = heart failure with a borderline left ventricular ejection fraction. HFpEF/HFnEF = heart failure with a preserved or normal left ventricular ejection fraction. Fig. 16.5.3.3 Heterogeneity of heart failure with normal left ventricular ejection fraction. Conceptually, the diagnosis of heart failure requires evidence of congestion: for example, elevated natriuretic peptides, evidence of a cardiac abnormality, and (retrospectively) an increased risk of cardiovascular events.

section 16 Cardiovascular disorders 3410 In patients aged over 50 years, ischaemic heart disease is the dom- inant cause of HFrEF and hypertension the dominant cause of HFnEF. There are many rare causes of heart failure (Table 16.5.3.2), but collectively these affect a substantial number of patients. Diagnosis Most heart failure is first diagnosed at a late stage in the disease, subsequent to a hospital admission. This is unlikely to change until screening the population at risk with natriuretic peptides becomes routine. There are six diagnostic steps: Step 1: Case ascertainment The first and most important step is suspecting that something might be wrong. The patient may complain of breathlessness, but this is a late manifestation of disease in a sedentary population. By the time orthopnoea, paroxysmal nocturnal dyspnoea, or breathlessness on mild exertion have developed, the disease is far advanced. Walking with the patient at a brisk pace may well provoke symptoms but does not lend itself to the organization of conventional clinics in primary or secondary care. Ankle oedema due to rising systemic venous pres- sure is also a late manifestation of disease and carries low specificity. Symptoms and signs may be abolished by diuretic therapy, but there is concern that such treatment may accelerate the progression of dis- ease by deleterious activation of neuroendocrine systems. Earlier detection of heart failure requires a provocative test of cardiac reserve (e.g. a corridor walking test) or identification of ac- tivated compensatory mechanisms (e.g. natriuretic peptides) in pa- tients deemed at risk of heart failure by virtue of age or medical risk factors. Any patient prescribed a loop diuretic should be presumed to have heart failure until proven otherwise. Table 16.5.3.2 Some rarer causes of heart failure Causes Comments Phenotype and specific therapy Amyloidosis Due to plasma cell expansion/myeloma (AL), transthyretin (ATTR) gene mutation or chronic infection/inflammation (AA). TTR mutations may cause 10% of HFpEF in older people Increased LV wall thickness, HFbEF, or HFpEF. Often atrioventricular conduction delay Poor prognosis for AL. Most patient die within a year of diagnosis. ATTR better prognosis. Specific therapies in discovery (e.g. tafamidis) Haemochromatosis High serum ferritin and transferrin saturation. Often diabetic. Affects c.0.05% of Northern Europeans HFrEF or HFbEF. Often a restrictive picture Treat with phlebotomy and iron chelation therapy. Early detection important Haemosiderosis Usually associated with multiple blood transfusions due to haemolytic or aplastic anaemia. Carcinoid syndrome Caused by hepatic or more rarely pulmonary metastasis of serotonin secreting tumours Tricuspid regurgitation and pulmonary stenosis leading to low output and peripheral congestion. Sarcoid heart disease Often associated with pulmonary disease HFrEF or HFpEF. Arrhythmias and conduction defects common Tachy-cardiomyopathy Ventricular rate usually persistently >150 bpm. Usually supraventricular but rarely ventricular tachycardia. Lower rates suggest that tachycardia is a consequence of heart failure Dilated cardiomyopathy. Resolves usually within a few weeks when arrhythmia is corrected Thyrotoxicosis May be iodine/amiodarone induced. Weight loss, tachycardia, and other features of thyroid hormone excess High output Phaeochromocytoma Due to catecholamine secreting tumours—usually adrenal HFrEF. Care with the use of adrenergic antagonists. Requires surgical correction Genetic DCM More than a dozen genetic mutations, notably of the titin gene HFrEF Lamin A/C gene mutation Rare HFbEF. Atrioventricular conduction defects, ventricular arrhythmias, and sudden death Muscular dystrophy Duchenne, Becker, and myotonic dystrophy HFrEF often with conduction defects Hypertrophic cardiomyopathy May be genetic or sporadic HFpEF or HFbEF Left ventricular
noncompaction May be familial HFrEF or HFbEF Endomyocardial fibrosis Usually a tropical disease possibly due to parasitic disease. Consider if eosinophilia HFpEF or HFbEF. Restrictive defect Iatrogenic Cancer chemotherapy, radiation, calcium channel blockers, hypoglycaemic therapies Anthracycline and radiation induced damage may be irreversible. May be HFrEF or HFpEF

Nutritional deficiency Thiamine, iron, selenium Rare unless severe deficiency Peripartum Cardiomyopathy Usually in last trimester or within a few weeks of delivery May only be recognized when severe. Usually recovers if patient survives. May recur with further pregnancy Myocarditis May be viral, including HIV, or due to borrelia (Lyme disease) or trypanosomiasis (Chagas disease). Giant cell myocarditis has a particularly poor prognosis HFrEF HIV—often pulmonary hypertension Chagas disease—arrhythmias Borrelia—consider doxycycline Giant cell—steroids?/immunosuppression?

16.5.3 Chronic heart failure 3411 Step 2: Proving that cardiac dysfunction and heart failure are present Once heart failure is suspected, objective evidence of cardiac dysfunction is required. Breathlessness and ankle swelling are not specific to heart failure. Signs of heart failure, such as jugular venous distension, are relatively specific but insensitive, often difficult to elicit, and not easily recorded in a way that convinces colleagues. Chest radiography is no longer regarded as essential. A normal chest radiograph is not uncommon in patients with heart failure, and radiographic cardiomegaly is frequently a spurious finding. The electrocardiogram (ECG) is almost universally abnormal in heart failure and if genuinely normal places the diagnosis in doubt. Until recently, echocardiography was considered the practical gold-standard measure for cardiac dysfunction and focused al- most exclusively on identifying valve disease and HFrEF. However, there is growing awareness of the limitations of echocardiography, especially when not interpreted by experts. Reproducibility of LVEF estimation is poor, and measurements of diastolic function are complex and often contradictory. Probably the best echocar- diographic guide to cardiac dysfunction, at least when chronic, are atrial volumes. Natriuretic peptides provide a simple approach to diagnosis and are more closely associated with atrial volumes than many other measures of cardiac dysfunction. They are not only more sensitive than cardiac imaging but a better guide to the patient's prognosis. Natriuretic peptides are also more specific than imaging when the question is 'Does this patient have serious disease requiring further investigation?' rather than 'Does this patient have cardiac dysfunction?' A normal plasma concentration of a natriuretic pep- tide in the absence of a diuretic effectively excludes heart failure with one uncommon exception—constrictive pericarditis. Gross obesity is associated with somewhat lower plasma concentrations of natriuretic peptides and diuretics may reduce them as they im- prove congestion. The N-terminal fragment of pro brain natri- uretic peptide (NT-proBNP) is stable for days in blood samples and therefore can be measured easily and inexpensively in primary or secondary care. Interpretation of results requires additional information. Atrial fibrillation and renal dysfunction are other common reasons for an increase in plasma natriuretic peptides concentrations. Clinical acumen supported by a measurement of natriuretic peptide is usually sufficient to make or refute a diag- nosis of heart failure. Step 3: Differential diagnosis If a patient has symptoms, merely excluding or diagnosing heart failure is not enough. Alternative causes of symptoms should be sought. The common differential diagnoses for breathlessness are lung disease, obesity, and being unfit, all of which may coexist with heart failure. Determining how much each is contributing to symp- toms will help guide use of diuretics; dehydrating patients with lung disease is unlikely to make them better and may make them worse. Spirometry may help identify lung disease, but low values may re- flect general frailty and poor technique rather than lung disease. Natriuretic peptides can help; a slim patient who is very breath- less but only has moderately elevated NT-proBNP is likely to have lung disease as the dominant pathology. Cardiopulmonary exercise testing aids differential diagnosis but requires special equipment and expertise. Echocardiographic evidence of mild diastolic dysfunction is very common in elderly people and heart failure can be

readily overdiagnosed. A diagnosis of HFnEF made on the isolated echocar- diographic finding of diastolic dysfunction should always be regarded with caution, and only following exclusion of alternative pathology. Conditions that may masquerade as ‘diastolic heart failure’, either in isolation or in combination, are listed in Table 16.5.3.3. Step 4: Cardiac phenotype and cause(s) of cardiac dysfunction Clinical acumen combined with natriuretic peptides may be enough to make a diagnosis of heart failure, but is a poor guide to cardiac phenotype. The workhorse of cardiac phenotyping is the echocardiogram. The echocardiogram provides an approxi- mate guide to LVEF and therefore differentiates HFrEF from HFnEF, identifies abnormal heart valves, and quantifies atrial vol- umes. Of the many parameters of diastolic function, increased left atrial size is probably the simplest and most reliable, and is an im- portant prognostic indicator regardless of baseline left ventricular function. For patients with HFrEF, the amount of myocardial scar is an important determinant of the response to treatment and is best as- sessed by CMRI. However, many heart failure services have little access to this investigation. Radionuclear imaging is an alternative. A diagnosis of coronary disease can usually be made based on the clinical history or, failing that, by CMRI, stress echo, or radionuclear imaging. In the absence of symptomatic angina there is no evidence that revascularization improves outcome in patients with chronic heart failure. The presence or absence of coronary disease should have little influence on the choice of pharmacological or device treatment, and there is no evidence that antiplatelet agents are safe or effective in this setting. Angiography should therefore be reserved for patients with limiting angina despite pharmacological therapy, and those presenting with heart failure in the context of an acute cor- onary syndrome. CT angiography can be used if it is felt necessary to exclude left main-stem disease or that of another proximal coronary artery. There is little information to be gained from heart catheter- ization that cannot be obtained more pleasantly, safely and at lower cost by noninvasive methods, which may also supply information that an angiogram cannot. Table 16.5.3.3 Conditions masquerading as diastolic heart failure COPD/Cor pulmonale (without RV dysfunction) Obesity-hypoventilation syndrome Obstructive sleep apnoea Severe renal disease Anaemia Thyrotoxicosis Nephrotic syndrome Silent myocardial ischaemia Venous insufficiency Lymphatic obstruction

 Step 5: Comorbidity—what other problems might exacerbate or complicate heart failure? Patients rarely only have heart failure. Identifying important cardio- vascular and noncardiovascular comorbidity provides additional therapeutic targets (Table 16.5.3.4). Step 6: Diagnostic tests required to achieve therapeutic aims The therapeutic goals should first be defined. If it is palliative care, then only treatments designed to control symptoms are appropriate (this may include diuretics, ACE inhibitors, mineralocorticoid antagonists (MRA), cardiac resynchronization therapy, and pos- sibly digoxin and intravenous iron). If the goal is to improve prog- nosis through ‘disease-modifying’ interventions, then β-blockers, ivabradine, and implantable cardiac defibrillators should be added to the list. Preventing patients with atrial fibrillation from developing the misery of a stroke might be considered appropriate regardless of other therapeutic aims. The small amount of information (10 items) routinely required to use these agents safely and effectively is shown in Table 16.5.3.5. Prognosis The prognosis of heart failure depends on the clinical context. Incident heart failure is associated with a 30% mortality at 6 months. The annual mortality of chronic stable patients is now probably less than 5% per annum, but admission to hospital with worsening heart failure has a mortality of about 10–15%, with mortality in the 6 months after discharge from an admission being in the range of 15–25%. Age is an important determinant of mortality, with the in- fluence of treatments shown in Fig.

16.5.3.4. Readmission rates are also high; most patients with heart failure will be admitted at least once in a 3-year period, and following a re- admission, 15–25% will have a further readmission within 30 days without expert support. Age is not such a good predictor of readmis- sion, perhaps because older people have a higher mortality. A pragmatic prognostic scoring system for chronic heart failure can be found at http://www.heartfailurerisk.org/, and may be im- proved by some simple additional pieces of information, such as whether the patient has had a recent exacerbation of symptoms, the dose of diuretic, and plasma concentration of NT-proBNP. Knowing prognosis can help with management, both in terms of advice to the patient and choice of therapy. Management Modern management of patients with heart failure requires the co- ordinated input of a multidisciplinary team of dedicated cardiolo- gists, specialist heart failure and rehabilitation nurses, primary care physicians, and palliative care specialists. The key to the successful Table 16.5.3.4 Common problems (comorbidities) complicating the diagnosis and management of heart failure Problem Comment Obesity (and lack
of fitness) Alternative cause for breathlessness creating diagnostic uncertainty and problems with judging diuretic dose. Diuresis will not help breathlessness due to obesity. Obesity is consistently associated with a better prognosis in a broad spectrum of patients with cardiovascular disease, including heart failure. Cachexia Ominous sign in heart failure. Exclude cancerous malignant disease. If patient is a candidate for transplant or mechanical assist, consider urgent referral. COPD Alternative cause for breathlessness creating diagnostic uncertainty and problems with judging diuretic dose. Diuresis will not help breathlessness due to COPD. Patients with heart failure and COPD have a worse prognosis. Atrial fibrillation AF may cause heart failure and vice versa. Optimal ventricular rate control may be about 80 bpm at rest. Need for anticoagulation. Ischaemic heart disease Common cause of a reduced LVEF. Little evidence that revascularization improves prognosis. Coronary angiography only indicated if patient has angina. Ongoing research into revascularization of viable myocardium but randomized controlled trials neutral so far. Hypertension A sign that the left ventricle still has some reserve. Most treatments for heart failure reduce blood pressure, so in this context hypertension is a good sign! Hypotension Often limits amount of pharmacological treatment and is a poor prognostic sign. Cardiac resynchronization will increase systolic blood pressure in appropriately selected patients. Anaemia Often associated with iron deficiency although not always corrected by oral or even intravenous iron. Some anaemia is dilutional (plasma volume expansion) and some caused by renal dysfunction and deficient erythropoiesis. Folate and B12 deficiency are rarely important causes of anaemia in heart failure. Diabetes mellitus Indicates a worse prognosis, possibly because of associated renal problems. Treatment for diabetes may make heart failure worse. Optimal HbA1c in patients with heart failure being treated for diabetes may be around 7.5% (lower if ‘prediabetic’). Chronic kidney disease Often due to pre-existing renal damage and exacerbated by hypotension and low renal blood flow. Often limits the doses of medication that can be given. Renal function is a powerful prognostic marker (more powerful than LVEF). Stroke Related mainly to pre-existing hypertension, atherosclerosis, and atrial fibrillation. Dementia Age often brings deterioration in cognitive as well as cardiac function. Dementia reduces ability for self-care and adherence to advice and medication. Worsening heart failure may impair cognitive function. Aortic stenosis Common in older people. Diuretics may reduce congestion and symptoms, but other medication may be of little help and may cause hypotension. Consider aortic valve surgery or transcutaneous procedure. Mitral regurgitation Common in all forms of heart failure. May improve with treatments that reduce ventricular volume, especially cardiac resynchronization. Patient selection for surgery often difficult. Transcutaneous repair may be considered.

16.5.3 Chronic heart failure 3413 management of these patients is prompt identification in the com- munity and following admission to hospital, and access to follow-up and management by a specialist team. Lifestyle Patients with heart failure should be advised to lead a healthy lifestyle, avoiding smoking and excessive alcohol consumption, eating a balanced diet, and taking regular exercise (http://www. heartfailurematters.org/en_GB). There is little evidence that such advice makes a difference to prognosis, but it probably improves well-being. Attention to psychological health is important. Keeping socially active, taking holidays (with adequate health insurance; http://www.bhf.org.uk/heart-health/living-with-aheart-condition/ living-with-heart-failure.aspx) and investing in hobbies and recre- ations are more important than pharmacological treatments for anxiety and depression that are, however, mostly safe. There is no evidence that complementary medicine can alter the course of heart failure but, provided the patient is not tempted to stop conventional therapy, it may provide them with psychological support. Patients should know what medication to take and be advised to have a system to ensure that they do so. Excessive dietary salt and fluid consumption should be avoided, but there is scant evidence that severe restriction of dietary salt is helpful and it might do harm. Fluid restriction (to <1.5 litres/day) may be required in patients with advanced, diuretic-resistant heart failure. The ideal body mass index for a patient with heart failure is probably about 30 kg/m2. Dieting to lose weight might improve symptoms, but there is no evidence that it will improve prognosis and it may be harmful. Patients with severe heart failure may develop cachexia (in the context of heart failure, this may mean achieving a normal body mass index) that may be partly due to reduced cal- orie intake. Trying to improve appetite seems reasonable, although of uncertain prognostic value and may not reverse weight loss. There is no evidence that supplementing the diet with vitamins or trace elements helps. Patients with heart failure are at increased risk of dying from in- fluenza and pneumococcal pneumonia and should receive these vaccinations, although there is no specific evidence that they alter outcome in patients with heart failure. It is important to be sensitive to the patient’s view of their illness. Many patients will not want to discuss how they are likely to die, others will. Developing counselling skills that allow patients to raise issues such as death and identifying when a patient has run out of therapeutic options and requires palliative care is an important part of a heart failure service. It is also important to address the worries and concerns of carers and the patient’s social network as this may help them to support the patient with issues such as adherence to medicine, keeping appoint- ments, or doing monitoring tests. Drug treatment of HFrEF The change in prognosis resulting from pharmacological and device therapy for patients with HFrEF (Table 16.5.3.5) is among the most remarkable success stories for any disease in the last quarter century (see Fig. 16.5.3.4). Loop and thiazide diuretics Diuretics are the most effective method of dealing with congestion, regardless of cardiac cause. They are also the most abused and least evaluated class of medication for heart failure. They are generally given at a fixed daily dose, but many patients can do without their diuretics for several days at a time, and others for much longer. Diuretic-free days may allow the patient greater freedom of activity. Some advocate adjusting the diuretic dose to maintain an ideal weight, which suits some patients. Reliable daily weight monitoring with accurate scales, potentially as part of a telemonitoring pro- gramme, may facilitate this strategy. In most countries, diuretics acting on the loop of Henle, which produce a powerful diuresis lasting a few hours, are preferred. Once the diuresis is over, avid renal salt and water retention occur. In some countries, thiazide diuretics acting on the distal convoluted tubule are preferred first-line agents. They produce a less powerful but much longer natriuresis, which may result in similar 24 h so- dium excretion to loop diuretics, but some patients will complain Table 16.5.3.5 Indications for therapy and information required for choosing and monitoring key

treatments in heart failure HISTORY EXAMINATION ELECTROCARDIOGRAM BLOOD TESTS ECHOCARDIOGRAM (evidence base for use) SOB (NYHA CLASS) BP OEDEMA HR AF QRS K GFR BNP HFrEF HFpEF (>40%) Loop diuretics II-IV X X X X Symptomatic Symptomatic ACE/ARB II-IV X X X Symptomatic/Prognostic Symptomatic ARNI II-IV X X X X Symptomatic/Prognostic ? β-Blocker II-IV X X X Prognostic ? MRA II-IV X X X Symptomatic/Prognostic (<35%) ? Ivabradine II-IV X X Symptomatic/Prognostic (<35%) ? Digoxin III-IV X X X X X Symptomatic ? Hydralazine/ Nitrates III-IV X Symptomatic/Prognostic ? ICD I-III

> 120 msec Prognostic (<35%) ? CRT II-IV X X 120 msec/LBBB Symptomatic/Prognostic (35%) ARNI, angiotensin receptor neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist; ICD, implantable cardiodefibrillator; CRT, cardiac resynchronization therapy; X indicates where information is required to guide treatment.

section 16 Cardiovascular disorders 3414 of an increase in nocturia and the rate of hypokalaemia and hyponatraemia may be higher. Thiazides are said to be ineffective when renal function is substantially impaired. In patients with hypertension, thiazide diuretics have repeatedly been shown to re- duce myocardial infarction, stroke, heart failure, and death. Similar evidence for loop diuretics is lacking. Typically, a patient will be initiated on 40 mg of furosemide or 1 mg of bumetanide per day. The patient should be warned that the first few doses are likely to provoke a marked diuresis, but that this will subside as pathophysiological signals for salt and water reten- tion intensify (the ‘braking’ effect). Diuretics may provoke urinary retention in patients with prostatic disease. Serum electrolytes and renal function should be monitored. If serum potassium drops below 4.0 mmol/litre, then a potassium-sparing diuretic should be given; usually an MRA. Patients with severe congestion may be treated with high doses of loop diuretics or with a combination of loop and thiazide diuretics. It is unclear which is the better strategy. An MRA may be added to either combination to prevent hypokalaemia and further enhance natriuresis. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and renin inhibitors Angiotensin-converting enzyme inhibitors Angiotensin-converting enzyme (ACE) inhibitors are one of the cornerstones of contemporary therapy for HFrEF. The onset of heart failure provokes the production of renin and, in turn, angiotensin II, which stimulates AT1 receptors that cause vasoconstriction, secre- tion of aldosterone, and sodium retention. Activation of the renin–angiotensin–aldosterone system (RAAS) is subtle until diuretics are given. ACE inhibitors block the production of angiotensin II. The ACE is also responsible for the breakdown of bradykinin, which may be responsible for side effects such as cough (much more common in women) and angioneurotic oedema. Bradykinin also stimulates the production of prostacyclin, which may be an important part of the mode of action of ACE inhibitors. Aspirin blocks the production of prostacyclin and may detract from benefit. ACE inhibitors improve symptoms and exercise capacity, have favourable effect on ventricular remodelling (disease progression), reduce the risks of atrial fibrillation and hospitalization for heart failure, and delay death by reducing the rate of both sudden death and death from progressive heart failure. In addition to idiosyncratic side effects such as cough and angio- neurotic oedema, ACE inhibitors usually reduce blood pressure and increase serum potassium and creatinine, each of which may be dose limiting. In patients with renal artery stenosis, the rise in serum creatinine may be marked. ACE inhibitors are

contraindicated in pregnancy or during breastfeeding and in patients with a history of angioneurotic oe- dema. They should be used with caution in patients with a low blood pressure, high serum potassium, or marked renal dysfunction. ACE inhibitors should be started at a low dose, typically enalapril 2.5 mg bd or ramipril 1.25 mg bd. If the patient has well-maintained blood pressure and renal function and frequent monitoring is possible (e.g. in hospital), then doses may be doubled every 48 h up to a target of 10–20 mg bd for enalapril or 5 mg bd for ramipril. Patients who do not achieve guideline target doses quickly may never achieve them unless the continuity of care is excellent. For more fragile patients, titration of ACE inhibitors at 2-week inter- vals with a blood test at each step is recommended. Having said this, dose-ranging studies of ACE inhibitors have failed to show a striking advantage to higher doses, although patients at the milder end of the spectrum may benefit more from higher doses, perhaps because they can tolerate them. Asymptomatic low blood pressure should not deter attaining guideline target doses, but excessive in- creases in potassium and creatinine require dose reduction or may occasionally prevent use of ACE inhibitors. See section on blood Fig. 16.5.3.4 Cumulative effect of drugs and device therapy on mortality in patients with symptomatic heart failure and LVEF less than 40% between the ages of 50 and 70 years (baseline mortality represented by that on diuretic therapy only). CRT-D, cardiac resynchronization therapy—defibrillator; ARA/ARB, angiotensin receptor antagonist/angiotensin receptor blocker; BB, β-blocker; ACEi, angiotensin converting enzyme inhibitor.

16.5.3 Chronic heart failure 3415 pressure in ‘Practical aspects of monitoring and management’ for further details. Angiotensin receptor blockers Angiotensin receptor blockers (ARBs) inhibit the binding of angio- tensin II to the AT1 receptor. The AT2 receptor is not blocked and there is some evidence that this may be beneficial. Bradykinin deg- radation is not blocked, hence ARBs do not cause cough or angio- neurotic oedema. Overall, ARBs appear to have similar benefits to ACE inhibitors, but the evidence is somewhat less convincing and so they are a second choice (e.g. for patients who have troublesome cough with an ACE inhibitor). It is possible that ARBs are only ef- fective when used in high doses. In general, dual therapy with ARB and ACE inhibitors should be avoided. Renin inhibitors A large trial of a renin inhibitor (aliskiren) as an alternative to or in addition to an ACE inhibitor (enalapril) did not support its use in either capacity, indeed the addition of aliskiren to enalapril led to more adverse effects without benefit. Angiotensin receptor–neprilysin inhibitors LCZ696 (valsartan/sacubitril) is a hybrid of an ARB (valsartan) and a neutral endopeptidase or neprilysin inhibitor, an enzyme respon- sible for inhibiting the degradation of both natriuretic peptides and bradykinin. A clinical trial comparing LCZ with enalapril in more than 8000 patients with HFrEF was stopped due to substantial benefit (about 20% reduction) on a composite end point of risk of death and hospitalization for heart failure. In terms of incorporation of valsartan/sacubitril into routine clinical practice, an analysis pub- lished in 2017 indicates that it is cost-effective. A trial of this drug combination in HfpEF is underway. Mineralocorticoid receptor antagonists Addition of an MRA to either an ACE inhibitor or an ARB has be- come another cornerstone of the contemporary management of HfrEF. Although ACE inhibitors and ARBs reduce the secretion of aldosterone, suppression is incomplete. MRAs block the effects of aldosterone much more effectively, and they improve symptoms and reduce hospitalizations and death due to worsening heart failure, re- duce the incidence of atrial fibrillation (presumably by treating con- gestion), and reduce the risk of sudden death (possibly by preventing hypokalaemia). All the benefits of MRAs may be explained by their ability to reduce urinary potassium and increase urinary sodium excretion and the associated fall in blood pressure. However, some believe that MRAs may also reduce myocardial fibrosis, but there is little evidence that MRAs improve

underlying myocardial function or remodelling. Spironolactone stimulates oestrogen receptors that may cause gy- naecomastia and testicular atrophy that become clinically problem- atic in about 10% of men. Eplerenone is more selective and does not cause these problems. MRAs should not be given to patients with a serum potassium greater than 4.9 mmol/litre and should be used with caution in pa- tients with substantial renal dysfunction or low blood pressure, also in frail elderly patients. Spironolactone and eplerenone should generally be started at 25 mg/day. Lower initial doses may be appropriate in older patients with impaired renal function (e.g. 25 mg on Monday, Wednesday, Friday—daily doses are unnecessary and splitting tablets can be problematic). The dose should be adjusted according to the effects on serum potassium, renal function, and blood pressure. The ideal serum potassium is around 4.5 mmol/litre. Doses of MRA should be increased to get serum potassium to this target, but reduced if potassium rises above 4.9 mmol/litre. Titration at 2-week inter- vals is generally appropriate unless the serum potassium is below 3.5 mmol/litre, in which case more urgent action is required. β-Blockers The sympathetic nervous system is activated in heart failure, leading to increases in heart rate, cardiac myocyte dysfunction, and weight loss (cachexia). Blockade of adrenergic receptors re- duces heart rate and reverses cardiac myocyte dysfunction, often leading to a remarkable recovery in myocardial function (although not scar), and it may retard, prevent, or reverse the development of cardiac cachexia. These effects lead to a reduction in mortality from worsening heart failure. Adrenergic receptor blockade also reduces the risk of supraventricular and ventricular arrhythmias, coronary events, and sudden death. How much of the benefit of β-blockers is mediated by reduction in heart rate or by other mechanisms is unclear. Recent analyses suggest that β-blockers may not be effective in patients with HFnEF and atrial fibrillation (see section on heart rate in ‘Practical aspects of monitoring and management’). Addition of a β-blocker to ACE inhibitor or ARB and an MRA (triple therapy) is the third cornerstone of the contemporary man- agement of HFrEF. Typically, an ACE inhibitor and β-blocker will be started in low doses at the same time. The dose of ACE inhibitor will be increased every day, week, or fortnight, but the β-blocker more slowly at 2–4-week intervals. MRAs are then added when titration of the ACE inhibitor and β-blocker are complete, but sooner if po- tassium is low or congestion is severe. β-Blockers are contraindicated in patients with bradycardia, im- paired atrioventricular conduction (unless the patient has a pace- maker), asthma (although not in most patients with chronic lung disease, who have little reversibility with sympathomimetic bron- chodilators), and in patients with severe uncontrolled congestion. Initiation of a β-blocker may cause some initial worsening of con- gestion and symptoms, but overcautious clinicians are probably a substantial reason for patient side effects and intolerance. There are many different β-blockers, but only four have been shown to be effective for HFrEF. Three are selective for the β1-receptor (bisoprolol, metoprolol succinate—not available in the United Kingdom—and nebivolol) and one is a nonselective agent (carvedilol). There is some evidence that carvedilol may be superior, and it is best studied in trials. β-blockers should be started at a low dose (e.g. carvedilol 3.125 mg bd or bisoprolol 1.25 mg once daily) and titrated upwards at 2–4- week intervals to target doses (carvedilol 25–50 mg bd or bisoprolol 10 mg/day). The optimal resting heart rate for patients in sinus rhythm appears to be 50–60 bpm, and doses should be adjusted to try to achieve this target. Achieving optimal heart rate appears more important than the dose of a β-blocker. In atrial fibrillation a ventricular rate of 75–85 bpm is associated with the best prog- nosis. Aggressive titration should be avoided if a β-blocker is used in atrial fibrillation. Fatigue and hypotension, or perhaps prescribing

section 16 Cardiovascular disorders 3416 inertia on the part of doctors, prevent many patients from achieving target doses. Ivabradine Ivabradine slows the rate of discharge of the sinus node, slowing heart rate only when the patient is in sinus rhythm. In patients with HFrEF and a resting sinus rate in excess of 70 bpm, ivabradine im- proves cardiac function and symptoms, and reduces hospitalization and death from worsening heart failure. It does not reduce arrhyth- mias or prevent sudden death. Ivabradine is indicated only when β-blockade has failed to re- duce sinus rate below 70 bpm. Many patients are perceived to be in- tolerant of doses of β-blockers required to control heart rate, but this can often be overcome by extra care and persuasion. Most patients with chronic lung disease tolerate β-blockers. Unlike β-blockers, ivabradine does not reduce blood pressure and has little or no effect on atrioventricular conduction. Younger patients with dilated car- diomyopathy may obtain larger benefits from ivabradine. Ivabradine is effective in patients who are unable to tolerate β-blockers, but they should be strongly encouraged to take at least a low dose of β- blocker in addition. Ivabradine is usually started at 5 mg bd and adjusted down to 2.5 mg bd or up to 7.5 mg bd to attain a resting heart rate of 50–60 bpm. Regarding side effects, the channels that ivabradine acts on are also present in the retina. Distortion of colour vision may occur, espe- cially while driving at night, but usually settles in a few weeks. Alternative vasodilators There is no certain place for other vasodilator agents in patients with heart failure. Although venous and arteriolar vasodilatation may have beneficial haemodynamic effects, there is little evidence that this improves symptoms or outcome. Vasodilatation may provoke further renal sodium retention and merely shunt blood through tis- sues, thereby reducing the useful work of the heart. For instance, there is evidence that both sildenafil and endothelin antagonists may increase pulmonary shunting in patients with heart failure, leading to a fall in arterial oxygen saturation, and similar shunting of blood may occur through peripheral tissues. Neither nitrates nor hydralazine used alone has been shown to improve symptoms or outcome in patients with heart failure, but when used in combination there is some evidence of benefit similar to that of ACE inhibitors, but potentially with less adverse effects on renal function. This combination is therefore sometimes used as an alternative to ACE inhibitors in patients with severe renal dysfunc- tion (e.g. eGFR <20 ml/min), but few patients are able to tolerate the high doses required. A study in patients of African-American origin suggested an improvement in morbidity and mortality when added to contemporary medical therapy including ACE inhibi- tors, β-blockers and MRA, but this finding has not been repeated in other racial groups. Vasodilator calcium antagonists have also failed to improve out- come, and other agents of this class, such as diltiazem and verapamil, have an adverse effect on outcome. Inotropic agents There is no firm place for any inotropic agent in patients with chronic heart failure. Whether digoxin has a contemporary role is uncertain because the trials of digoxin demonstrating modest benefit were conducted before the widespread introduction of β- blockers and MRA. These agents might have rendered digoxin ob- solete, but also might have made it safer and more effective. Digoxin has vagomimetic effects, slowing sinus rate and prolonging atrio- ventricular conduction, and therefore slowing ventricular rate in pa- tients with sinus rhythm or atrial fibrillation. It is also a diuretic. It does not drop and may increase blood pressure. For digoxin-naive patients with severe heart failure, an initial loading dose that does not need to be adjusted for renal dysfunction is appropriate. Maintenance doses should be adjusted according to renal function, erring on the side of caution in older people. The contemporary fashion is to use lower maintenance doses of digoxin, typically 125 micrograms/day for a middle-aged patient of average build and with good renal function, and 62.5 micrograms/day for older, frailer patients. Monitoring of serum digoxin is rarely ne- cessary, but it is important to check for and prevent hypokalaemia, which increases the risk of digoxin-induced arrhythmia.

Antiarrhythmic agents Amiodarone and dronedarone should only be given after expert advice and should be discontinued unless there is a clear need. In patients with moderate or severe HFrEF, addition of these agents to contemporary therapy increases mortality. They have a limited role in maintaining sinus rhythm in atrial fibrillation, and for the symptomatic treatment of ventricular tachycardia. Side effects such as pulmonary fibrosis or hepatitis are rare, pro- vided the maintenance dose of amiodarone is 200 mg/day or less. Photosensitivity and hypothyroidism are problems with long- term treatment. Other antiarrhythmic agents should generally be avoided in heart failure as they have adverse effects on cardiac function and prognosis. Lipid-modifying therapies There is no established role for lipid-modifying therapies in patients with heart failure. Two large trials of rosuvastatin failed to show a reduction in mortality, although some reduction in hospitalizations was observed. Considering all of the evidence, it is likely that pa- tients with less severe cardiac dysfunction (e.g. NT-proBNP <1000 ng/litre) do benefit from statins, but that patients with more ad- vanced disease do not. Some argue that treatment should be ration- alized and statins withdrawn. Others argue that there is no evidence of harm and some evidence for a reduction in morbidity, and that they should be continued. Informed patients may wish to express an opinion. One large trial suggested a small reduction in mortality with the addition of omega-3 fatty acids to contemporary heart failure therapy, but this awaits confirmation. Anticoagulants and antiplatelet agents Patients with heart failure and paroxysmal or persistent atrial fib- rillation should be anticoagulated. Warfarin has been the mainstay for many decades, but newer agents that do not require thera- peutic monitoring may be less likely to cause intracranial bleeding. Antiplatelet therapies are not effective in reducing emboli and markedly increase the risk of bleeding when used concomitantly with anticoagulants. They should usually be withdrawn when anti- coagulants are introduced, unless the patient has had a recent car- diac procedure.

16.5.3 Chronic heart failure 3417 There is no evidence that anticoagulant or antiplatelet agents, including aspirin, improve outcome in patients with heart failure in sinus rhythm, whether or not they have coronary artery disease. There are theoretical concerns about the safety of aspirin in patients with heart failure, but no robust evidence to refute or support its use. Aspirin might be partly responsible for iron deficiency anaemia now frequently observed in patients with heart failure. Medicines to avoid Some medicines should be avoided because evidence of benefit is lacking. Aspirin, statins, and omega-3 fatty acids might fall into this category. Other agents are harmful. For patients with HFrEF, rate- limiting calcium channel blockers increase morbidity and mortality. Oral hypoglycaemic agents may cause fluid retention, probably by increasing renal insulin sensitivity, or exacerbate heart failure in other ways. Metformin is relatively contraindicated in chronic kidney disease (eGFR <30) in heart failure because of an increased risk of lactic acidosis, although this is rare. Nonsteroidal anti- inflammatory drugs, including aspirin, may cause worsening renal function and hyperkalaemia. Paracetamol and opioids are the pre- ferred analgesics. Many cancer chemotherapies are associated with cardiac toxicity. Amiodarone and dronedarone should be avoided unless there is a clear indication. Other medicines in development The failing heart has a shortened ejection time. Omecamtiv mecarbil is a cardiac myosin activator that prolongs the duration of systole and therefore increases stroke volume and efficiency. Positive results have been reported in Phase I and Phase II studies. The effects on vascular events and mortality in patients with heart failure of adding a low dose of rivaroxaban (a factor Xa antagonist) to background therapy (usually including aspirin) is being studied. Soluble guanylate cyclase inhibitors and stimulators, novel MRAs, vaptans, nitroxyl donors, ryanodine channel stabilizers, agents acting on the mitochondrial respiratory chain, and superabsorbent polymers are among a

substantial array of compounds under investigation. Gene therapy and stem cells The potential to improve cardiac myocyte function by transfecting cells with the SERCA2a (to improve calcium uptake of the sarco- plasmic reticulum), ribonucleotide reductase (to increase synthesis of dATP), and a variety of other genes is being explored. Similarly, efforts are being made to use a variety of stem cells to induce cardiac regeneration. Such approaches have met with little success thus far. Treatment of HFrEF with devices Implantable cardioverter–defibrillators Most patients with mild to moderate heart failure will die sud- denly rather than progress gradually to terminal disease. Sudden death is often due to a ventricular arrhythmia, either spontaneous or provoked by myocardial ischaemia or infarction. Implantable cardioverter–defibrillators (ICDs) deliver pacing and shock therapy to terminate ventricular arrhythmias. ICDs reduce the rate of sudden death by about 70% and lead to a 1–2% absolute annual reduction in all-cause mortality, hence a pa- tient has to avoid dying of other things for quite a long time before benefiting substantially from an ICD, which does not improve and may impair symptoms and quality of life. The risk of inappro- priate shocks has declined dramatically after much longer device- diagnostic delays were introduced prior to delivering ICD therapy. Forcing ICDs to hesitate before they intervene has revealed that most ventricular tachycardia self-terminates. The ideal candidate for an ICD has mild heart failure, a low ejec- tion fraction, and a QRS duration exceeding 120 ms, which is similar to the criteria for implanting a cardiac resynchronization therapy (CRT) device. Indeed, it is possible that patients who are not can- didates for CRT have little to gain from an ICD. Implanting a CRT device rather than an ICD in an appropriate patient may increase the benefit of the ICD component of therapy, although CRT alone can reduce sudden death. In summary, there is no doubt that ICDs reduce sudden death and all-cause mortality, but there are grave doubts about their cost-effectiveness in the absence of a concomi- tantly implanted CRT. Cardiac resynchronization therapy In appropriately selected patients, CRT improves ventricular func- tion, reduces mitral regurgitation, raises blood pressure, improves symptoms and quality of life, reduces recurrent hospitalization for heart failure, and increases longevity substantially by reducing the rate of both sudden death and end-stage heart failure. Adding an ICD function to a CRT device may prevent some sudden deaths and provide modest incremental benefit to CRT alone. Current evidence suggests that patients with HFrEF (up to an LVEF of 40%) in sinus rhythm with a QRS duration of more than 140 ms, who have been stabilized on optimal medical therapy, are likely to benefit from CRT regardless of the severity in symptoms. Patients with a QRS duration between 130 and 140 ms may get some benefit, but patients with a QRS duration of less than 130 ms may be harmed by CRT. Patients with ischaemic heart disease have less improvement in cardiac function than patients with dilated cardio- myopathy but similar prognostic benefit. It is not clear whether QRS morphology is important, although left bundle branch block is associated with longer QRS duration which is, in turn, associated with a better response to CRT. Whether patients with atrial fibrillation (AF) benefit from CRT is controver- sial, although some advocate CRT with atrioventricular node abla- tion. There are many uncertainties about the optimal programming of devices. Expert advice should be sought for patients who have had a disappointing response to CRT. Comorbidity and its impact on management
of heart failure Valve disease Valve repair or replacement should be considered for all patients with heart failure and substantial mitral or aortic valve disease. Pharmacological treatment, other than for the treatment of conges- tion, will make little difference to symptoms, disease progression, or prognosis in the presence of substantial aortic or mitral stenosis. Patients with aortic stenosis should be considered for aortic valve surgery or transarterial aortic valve implantation. Mitral regurgita- tion is often functional due to left ventricular dysfunction. Although severe mitral

regurgitation due to structural disease may benefit from surgical repair, the results of surgery for functional mitral

section 16 Cardiovascular disorders 3418 regurgitation are less certain. Transcutaneous procedures to reduce mitral regurgitation have met with some success, but surgical cor- rection of tricuspid regurgitation is of dubious benefit and carries substantial risk. Pulmonary valve disease is not common. Diuretics may relieve the symptoms of congestion in patients with aortic or mitral regurgitation for long periods, allowing the disease to pro- gress beyond the optimal timing of surgery. Renal dysfunction Renal dysfunction is a bad prognostic sign in heart failure and yet many agents that improve prognosis cause a decline in glomerular filtration rate. Clearly, at some point there will be a trade-off between the benefits of therapy and their adverse effect on renal function. Precisely where that point lies is unknown. Patients with renal dys- function are prone to developing hyperkalaemia. Renal dysfunction often precedes the development of heart failure, perhaps reflecting the damage that hypertension has done to both heart and kidney. Many patients will have renal artery ath- eroma. Low arterial and high venous pressures conspire to produce a low net renal perfusion pressure, which is a major determinant of renal function. The introduction of an ACEi or ARB often causes a rise in serum creatinine, and an increase of up to 30% is generally regarded as acceptable provided renal function subsequently stabilizes. Many medicines are excreted by the kidney and therefore lower doses are required to obtain plasma concentrations similar to those in people with normal renal function. Improving the net renal perfusion pressure, avoiding non- steroidal anti-inflammatory drugs (NSAIDs; including aspirin), stopping non-ACEi/ARB antihypertensive agents, and—if this fails—allowing efferent renal arteriolar tone to increase by re- ducing or stopping ACE inhibitors or ARBs are the best hope of improving renal function. Methods of increasing blood pressure are discussed later in the chapter. Diuretics and nitrates can reduce both arterial and venous pressure and their effects on renal func- tion are unpredictable, but usually adverse unless venous pressure is high and falls substantially with treatment. In practice, if con- gestion is not severe, reducing the dose of diuretic should be the first response to declining renal function. Only if this fails or is inappropriate should the dose of ACE inhibitor/ARB be reduced or stopped. Ultrafiltration or renal dialysis can be used to lower serum creatinine and potassium, but neither intervention is proven to prolong survival, although they may bridge a patient to a de- finitive procedure (e.g. mechanical circulatory support), which can also improve renal function when this is due to severe heart failure and itself be a bridge to a more permanent solution (i.e. transplantation). Respiratory disease Patients who have a definite diagnosis of asthma should avoid β- blockers; ivabradine may be similarly effective to β-blockers for patients in sinus rhythm. Most patients with chronic obstructive pulmonary disease tolerate and benefit from β-blockers. Monitoring of airways obstruction by spirometry may be appro- priate when in doubt. This may also provide an opportunity to with- draw unnecessary bronchodilator therapy. Patients with pulmonary fibrosis may have persistent fine crepitations at the lung bases that may be confused with pulmonary oedema and lead to overaggressive diuretic therapy. Sleep-disordered breathing Patients with heart failure are prone to both obstructive and cen- tral sleep apnoea, and many will have both. The severity of sleep- disordered breathing may vary according to the severity of congestion or the reduction in cardiac output, sleeping posture, or the effects of alcohol or hypnotic or anxiolytic agents. Simple ambu- latory equipment is available for diagnosis. Arterial oxygen desat- uration is probably the key manifestation of important disease, but arrhythmias induced by airways obstruction may also be important. Studies of continuous positive airways pressure ventilation have been disappointing, possibly because high intrathoracic pressures can reduce

cardiac output and increase right-sided congestion. A major trial using adaptive servoventilation showed that this treat- ment increased mortality. Angina and myocardial ischaemia There is no evidence that revascularization reduces morbidity or mortality in patients with heart failure and coronary artery disease. Pharmacological treatment of angina is appropriate in the first in- stance, which may include β-blockers, ivabradine, and short-and longer acting nitrates. Ranolazine may also be used, although the evidence base is limited. Vasodilator calcium antagonists should be used cautiously and avoided if blood pressure is low. For patients with persistent, limiting angina, coronary angiog- raphy and revascularization should be considered. There is anec- dotal evidence that revascularization of silent myocardial ischaemia or viable but dysfunctional myocardium may have striking benefits for cardiac dysfunction and symptoms of heart failure, but two ran- domized trials have failed to show that this strategy is generally su- perior to pharmacological therapy. There is no imperative, based on current evidence, to investigate for ischaemia or to do a coronary angiogram that may set in train a series of events that the patient and clinician may regret. Atrial fibrillation About 50% of patients with AF also have heart failure, and at least 25% of patients with heart failure have AF. Patients with AF and heart failure should be anticoagulated (see ‘Anticoagulants and antiplatelet agents’, earlier). Clinical trials show no benefit from β-blockers in patients with AF and HFrEF, perhaps due to excessive reduction in ventricular rate. The optimal resting ventricular rate (measured at clinic rather than by ambulatory monitoring) in AF may be 75–85 bpm. Digoxin can improve ventricular rate control but is rarely required. Its vagomimetic properties provide better resting and nocturnal ven- tricular rate control, while β-blockers reduce the rise in ventricular rate during exercise. There is little evidence to support pulmonary vein ablation to re- store sinus rhythm in chronic heart failure. Patients in AF cannot benefit from atrioventricular (AV) resynchronization, and there is no good evidence that CRT is effective when AF is present. Patients who require a pacemaker or a defibrillator should be considered for AV node ablation and biventricular pacing, although the evidence for this strategy is not robust. CRT should be considered an inter- vention of last resort in the setting of AF.

16.5.3 Chronic heart failure 3419 Anaemia Anaemia in heart failure is often due to iron deficiency, which affects up to 50% of patients with this condition and is associated with poor quality of life, impaired exercise tolerance, and increased mortality. Serum ferritin may be elevated due to the fact that inflammation is part of the heart failure syndrome, hence in this patient group iron deficiency is typically recognized by serum ferritin less than 100 ng/ ml, or serum ferritin 100–300 ng/ml along with transferrin satur- ation less than 20%. The reasons for iron deficiency are unclear and may be related to reduced iron intake (anorexia), impaired intestinal absorption (mu- cosal oedema, reduced intestinal blood flow, disrupted iron uptake processes), increased gastrointestinal losses (gastritis, perhaps ex- acerbated by aspirin) and frequent venepuncture. Trials that have given oral iron alone (as the control arm of studies giving both oral iron and erythropoiesis stimulating agents) have shown that this has no effect on haemoglobin level, symptom se- verity, or exercise tolerance. By contrast, in randomized studies, intravenous iron has been shown to improve exercise capacity, car- diac function, symptom severity, and quality of life. Patients with symptomatic heart failure should be monitored regularly for the presence of iron deficiency and given intravenous iron if this is present. Anaemia is rarely due to folate or B12 deficiency. Many patients have impaired renal function and are either deficient in or resistant to erythropoietin, or have plasma volume expansion leading to ‘dilutional’ anaemia. Administration of erythropoiesis-stimulating agents increases haemoglobin and produces modest improvement in ejection fraction, exercise duration, quality of life, and heart failure-related hospitalizations, but is not proven to

affect mortality. Gout Gout is common in patients receiving diuretics for heart failure. Acute attacks should be treated with colchicine or steroids. NSAIDs should be avoided if at all possible. High-dose paracetamol or even opiates are preferred analgesics. Once an acute attack has settled, allopurinol may be used to reduce the formation of uric acid and the risk of recurrent attacks. Particular circumstances End-stage heart failure For patients with severe intractable heart failure, palliative care, mechanical circulatory support with left ventricular assists devices, or heart transplantation should be considered. Early referral of patients potentially appropriate for the latter therapies to an expert centre is warranted. Usually, these patients will be aged less than 70 years with no other serious, irreversible disease. Always consider the following: • Review pharmacological and device therapy; ensure optimal treat- ment and withdraw what is unnecessary or harmful. • Check for anaemia and iron deficiency. • Consider adding digoxin (a rapid loading dose may be appropriate). • Opiates might improve breathlessness. Exacerbation of chronic heart failure Heart failure is often portrayed as an inexorably progressive condi- tion with a poor prognosis. This is no longer true for many patients receiving modern treatment. Stabilization for a decade or more, remission and—for a lucky few—medical cure is now well docu- mented. However, many patients do deteriorate, even if well man- aged. The reasons are diverse and often remediable. Sudden acute deterioration in a previously stable patient may be due to infection, myocardial ischaemia or infarction, arrhythmias (especially AF), or (rarely) catastrophic failure of a heart valve. Failure to comply with advice on diet or to take prescribed medi- cines, anaemia, renal dysfunction, or poorly controlled hyperten- sion are more often subacute and should be detected long before the patient reaches an acute crisis. Treatment of heart failure with a normal ejection fraction (HFnEF) No treatment has been conclusively shown to alter the natural his- tory of HFnEF. However, diuretics relieve congestion and congestion can kill. Indeed, treatments directed predominantly at congestion, such as ACE inhibitors and MRA, may produce similar benefits in patients with HFnEF and HFrEF, provided the patient with HFnEF does have evidence of congestion (i.e. a raised plasma concentration of natriuretic peptides). The same may not be true of β-blockers: re- duction in heart rate will increase the duration of diastole that may be advantageous when the problem is impaired cardiac myocyte re- laxation, but deleterious when the problem is myocardial fibrosis and restriction. There is some evidence that digoxin reduces the risk of hospitalization for heart failure. There is little evidence for the safety or efficacy of calcium channel blockers. Hypertension and anaemia are common in this population, and are therapeutic tar- gets. The effects of angiotensin receptor–neprilysin inhibitors, sol- uble guanylate cyclase inhibitors, and interatrial septal shunt devices and many other interventions are currently being explored in this population. Practical aspects of monitoring and management Regular monitoring of symptoms, weight, and vital signs is essen- tial for good management, especially in sicker, unstable patients. Patients should be encouraged to do this for themselves, potentially assisted by a home telemonitoring system linked to expert clin- ical surveillance and advice, and supported by family and informal carers. Serum electrolytes and renal function should be measured at least every 6 months, and much more frequently in patients with ad- vanced or unstable disease. QRS duration and haemoglobin should be measured on at least an annual basis. There is little evidence to support routine serial echocardiography. There is some evidence to support serial monitoring of natriuretic peptides to identify patients who are in need of more intensive therapy. Symptoms and signs The clinical trials on which guidelines are based focus on morbidity and mortality, but symptoms are usually the reason why the patient seeks medical help. Fortunately, treatment can usually control symp- toms for most patients for most of the time. Less than 5% of patients with heart failure have severe end-stage symptoms at any time; most of these patients either improve or die within a few weeks. Heart rate A reduction in parasympathetic

and increase in sympathetic tone are responsible for the increase in heart rate in heart failure. β-blockers

section 16 Cardiovascular disorders 3420 and digoxin will reduce ventricular rate regardless of heart rhythm; ivabradine only if the patient is in sinus rhythm. For patients with HFrEF, the target range for resting heart rate in sinus rhythm is 50– 60 bpm, but for AF it is 75–85 bpm. Blood pressure High blood pressure is an important risk factor for developing heart failure, especially HFnEF. Low blood pressure is a bad prognostic sign, perhaps because it reflects more severe impairment in the pumping action of the heart (cardiac power output). Many medi- cines that reduce morbidity and mortality also lower blood pressure. Identifying the appropriate blood pressure for the individual patient, and achieving it, is a key aspect of managing heart failure. For most patients, treatment of heart failure will reduce systolic blood pressure below 140 mm Hg. Treatment of hypertension may cause the features of heart failure to disappear and may account for much of the confusion and uncertainty surrounding HFnEF as a clinical entity. A patient may be admitted in florid heart failure with a systolic blood pressure greater than 200 mm Hg, but after treatment, usually with diuretics and ACE inhibitors, there may be little residual evidence for heart failure even when diuretics are withdrawn. A low blood pressure that is not causing problems should not deter the patient or clinician from titrating medication to guideline- indicated doses. Patients may tolerate a systolic blood pressure of 80 mm Hg or less, but postural hypotension is likely to become a limiting factor, also rise in serum creatinine presumably attribut- able to reduced glomerular filtration due to reduced renal perfusion. When low blood pressure is a problem, then treatments for heart failure that increase blood pressure may be added, or treatments that reduce blood pressure reduced in dose or withdrawn. If the patient's symptoms and signs of heart failure are well controlled, the preferred action is to reduce the dose of diuretic. If symptoms and signs are not well controlled, then digoxin or CRT (if appropriate) will increase systolic blood pressure. If the aforementioned are in- appropriate or fail, then reducing the dose of disease-modifying therapies should be considered, with the potential benefits and risks explained to the patient. If the patient is oedematous, then the dose of β-blocker should be reduced, allowing heart rate to rise to around 80/min if in AF or, if in sinus rhythm, using ivabradine to keep resting heart rate at 50–60 bpm. If serum creatinine is in excess of 200 μmol/litre, then the dose of ACE inhibitor should be reduced. If serum potassium is in excess of 5 mmol/litre, then the dose of MRA should be reduced. If appropriate, referral for assess- ment for mechanical circulatory support or heart transplantation may be considered. Blood tests Patients with heart failure receiving diuretics should have a blood test at intervals not exceeding 6 months. Serum potassium For patients with HFrEF, mortality climbs steeply when potassium drops below 4.0 mmol/litre or rises above 4.9 mmol/litre. Aiming for a serum potassium of about 4.5 mmol/litre, usually by manipulating the dose of MRA, appears ideal. Potassium supplements are rarely necessary and should be used only short term. Patients with HFnEF may benefit similarly from this strategy. Renal function Serum urea and creatinine are stronger markers of prognosis than measures of cardiac dysfunction such as LVEF. As already noted, most treatments that improve the prognosis of heart failure cause a decline in renal function. Advice on manipulation of therapy to optimize renal function is provided in the section on blood pressure. Haemoglobin Anaemia, often due to iron deficiency, is common in patients with heart failure and indicates a poor prognosis. Treatment may improve symptoms and perhaps prognosis. Haemoglobin should be meas- ured at least annually. The electrocardiogram Most patients with HFrEF will have a QRS duration greater than 100 ms, and each year some of these will develop a QRS duration greater than 140 ms, indicating the need for CRT. Treatment with β-blockers will often mask the onset of AF, requiring anticoagulation and a change in strategy of

heart rate control. Patients should gen- erally have an annual ECG. Table 16.5.3.6 Example care plan context: recovering in hospital from episode of worsening heart failure Mandatory information (Unchanging) • Date of birth: 07/01/1943 • Sex: female • Height: 160 cm Mandatory information (most recent with date) • Aetiology: ischaemic heart disease • Most recent MI: yes: anterior 09/11/2005 • Comorbidity: type 2 diabetes, arthritis • LVEF: 32% (HFrEF) • Mitral regurgitation: moderate • Other important valve disease: no • Heart rhythm: sinus • PR interval: 210 msec • QRS duration: 110 msec • Device: none • FEV1: 2.1 (83% of predicted) • FEV1/FVC: 75% • Haemoglobin: 10.8 g/dl • Haematinic screen: to be done • HbA1c: 7.4% • Sodium: 138 mmol/litre • Potassium: 4.0 mmol/litre • Urea: 11.5 mmol/litre • Creatinine: 137 umol/litre • Albumin: 44 g/dl • NT-proBNP: 3742 ng/litre

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