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ESC Guidelines

Guidelines for the diagnosis and treatment of Chronic Heart Failure: full text (update 2005)

The Task Force for the diagnosis and treatment of CHF of the European Society of Cardiology

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Preamble

Guidelines and Expert Consensus Documents aim to present all the relevant evidence on a particular issue in order to help physicians to weigh the benefits and risks of a particular diagnostic or therapeutic procedure. They should be helpful in everyday clinical decision-making.

A great number of Guidelines and Expert Consensus Documents have been issued in recent years by the European Society of Cardiology (ESC) and by different organizations and other related societies. This profusion can put at stake the authority and validity of guidelines, which can only be guaranteed if they have been developed by an unquestionable decision-making process. This is one of the reasons why the ESC and others have issued recommendations for formulating and issuing Guidelines and Expert Consensus Documents.

In spite of the fact that standards for issuing good quality Guidelines and Expert Consensus Documents are well defined, recent surveys of Guidelines and Expert Consensus Documents published in peer-reviewed journals between 1985 and 1998 have shown that methodological standards were not complied with in the vast majority of cases. It is therefore of great importance that guidelines and recommendations are presented in formats that are easily interpreted. Subsequently, their implementation programmes must also be well conducted. Attempts have been made to determine whether guidelines improve the quality of clinical practice and the utilization of health resources.

The ESC Committee for Practice Guidelines (CPG) supervises and coordinates the preparation of new Guidelines and Expert Consensus Documents produced by Task Forces, expert groups, or consensus panels. The chosen experts in these writing panels are asked to provide disclosure statements of all relationships they may have which might be perceived as real or potential conflicts of interest. These disclosure forms are kept on file at the European Heart House, headquarters of the ESC. The Committee is also responsible for the endorsement of these Guidelines and Expert Consensus Documents or statements.

Classes of recommendations

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

*Use of class III is discouraged by the ESC.

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

The Task Force has classified and ranked the usefulness or efficacy of the recommended procedure and/or treatments and the Level of Evidence as indicated in the following tables:

Diagnosis of chronic heart failure

Introduction

Methodology

These guidelines are based on the Diagnostic and Therapeutic Guidelines published in 1995, 1997, and renewed in 2001,[1–3] which has now been combined into one manuscript. Where new information is available, an update has been performed whereas other parts are unchanged or adjusted only to a limited extent.

The aim of this report is to provide updated practical guidelines for the diagnosis, assessment, and treatment of heart failure for use in clinical practice, as well as for epidemiological surveys and clinical trials. Particular attention in this update has been allocated to diastolic function and heart failure with preserved left ventricular ejection fraction (PLVEF). The intention has been to merge the previous Task Force report[4] with the present update.

The Guidelines are intended as a support for practising physicians and other health care professionals concerned with the management of heart failure patients and to provide advice on how to manage these patients, including recommendations for referral. Documented and published evidence on diagnosis, efficacy, and safety is the main basis for these guidelines. ESC Guidelines are relevant to 49 member-states with diverse economies and therefore recommendations based on cost-effectiveness have been avoided in general. National health policy as well as clinical judgement may dictate the order of priority of implementation. It is recognized that some interventions may not be affordable in some countries for all appropriate patients. The recommendations in these guidelines should therefore always be considered in the light of national policies and local regulatory requirements for the administration of any diagnostic procedure, medicine, or device.

This report was drafted by a Writing Group of the Task Force (see title page) appointed by the CPG of the ESC. The draft was sent to the Committee (see title page) and after their review the document was approved for presentation. The full document as presented here is followed by an executive summary, which is published in the *European Heart Journal*. An evidence-based approach to the evaluations has been applied including a grading of the evidence for recommendations. However, for the diagnosis, evidence is incomplete and in general based on consensus of expert opinions. Already in the 2001 version, it was decided not to use evidence grading in this part. The same approach has been used here.

Major conclusions or recommendations have been highlighted by bullets.

Epidemiology

- Much is now known about the epidemiology of heart failure in Europe but the presentation and aetiology are heterogeneous and less is known about differences among countries.

Estimates of the prevalence of symptomatic heart failure in the general European population range from 0.4 to 2%.[5] The prevalence of heart failure increases rapidly with age,[6] with a mean age of the heart failure population being 74 years and, as the proportion of the population that is elderly is increasing, this partly accounts for the rising prevalence of heart failure.[7–10] Unlike other common cardiovascular diseases, the age-adjusted mortality attributed to heart failure also appears to be increasing. The ESC represents countries with a population of over 900 million, suggesting that there are at least 10 million patients with heart failure in those countries. Many patients with heart failure have symptoms and PLVEF.[11] There are also patients with myocardial systolic dysfunction without symptoms of heart failure and who constitute approximately a similar prevalence.[5,12] The prognosis of heart failure is uniformly poor if the underlying problem cannot be rectified. Half of patients carrying a diagnosis of heart failure will die within 4 years, and in patients with severe heart failure $>$50% will die within 1 year.[7,9] Studies have confirmed the poor long-term prognosis.[13–15] Recently, a report on heart failure in Scotland provided survival rates after hospital discharge from 1986 to 1995 suggesting improved prognosis over time.[16] Similar and more conclusive evidence of improvements has been reported from Sweden[17] and UK.[18]

The accuracy of diagnosis by clinical means alone is often inadequate,[19,20] particularly in women, elderly, and obese. To study properly the epidemiology and prognosis and to optimize the treatment of heart failure, the uncertainty relating to the diagnosis must be minimized or avoided completely.

Descriptive terms in heart failure

Acute vs. chronic heart failure

The term acute heart failure (AHF) is often used exclusively to mean new onset acute or decompensation of chronic heart failure (CHF) characterized by signs of pulmonary and/or peripheral congestion, including pulmonary oedema and/or peripheral oedema with or without

signs of peripheral hypoperfusion. Other forms of AHF include hypertensive AHF, pulmonary oedema, cardiogenic shock, high output failure, and right heart failure.

Various other classifications for AHF as a syndrome are utilized in coronary and intensive care units, which guide the treatment or are used in clinical research protocols.[21]

CHF, often punctuated by acute exacerbations, is the most common form of heart failure. A definition of CHF is given succeedingly.

The present document will concentrate on the syndrome of CHF and leave out aspects on AHF.[21] Thus, heart failure, if not stated otherwise, is referring to the chronic state.

Systolic vs. diastolic heart failure

As ischaemic heart disease is the commonest cause of heart failure in industrialized societies, most heart failure is associated with evidence of left ventricular systolic dysfunction, although diastolic impairment at rest is a common if not universal accompaniment. Diastolic heart failure is often diagnosed when symptoms and signs of heart failure occur in the presence of a PLVEF (normal ejection fraction) at rest. Predominant diastolic dysfunction is relatively uncommon in younger patients but increases in importance in the elderly. PLVEF is more common in women, in whom systolic hypertension and myocardial hypertrophy with fibrosis are contributors to cardiac dysfunction.[11,22]

A large proportion of patients with CHF have PLVEF as judged by resting left ventricular ejection fraction (LVEF).[11,23] Patients with acute pulmonary oedema may also have normal LVEF.[24] However, the pathophysiology of heart failure in patients with normal ejection fraction is probably heterogeneous. In most cases, heart failure may be caused mainly by diastolic dysfunction, but some patients have reduced systolic atrioventricular plane displacement, indicating mild systolic dysfunction; in some other cases excessive arterial stiffening has been reported.[25] Furthermore, most, if not all patients with systolic dysfunction, have associated changes in diastolic function. Therefore, in most cases, diastolic and systolic heart failure should not be considered as separate pathophysiological entities. In some patients, however, it appears that the diastolic dysfunction dominates and may be a more sensitive marker of heart disease than LVEF. The most common aetiologies are hypertension, coronary artery disease, or both, whereas hypertrophic cardiomyopathy is a more unusual but important aetiology.[11,22]

Other descriptive terms in heart failure

Right and left heart failure refer to syndromes presenting predominantly with congestion of the systemic or pulmonary veins. The terms do not necessarily indicate which ventricle is most severely damaged. High- and low-output, forward and backward, overt, treated, and congestive are the other descriptive terms still in occasional use; the clinical utility of these terms is descriptive without aetiological information and therefore of little use in determining modern treatment for heart failure. Mild, moderate, or severe heart failure is used as a clinical symptomatic description, where mild is used for patients who can move around with no important limitations of dyspnoea or fatigue, severe for patients who are markedly symptomatic and need frequent medical attention, and moderate for the remaining patient cohort.

Definition of CHF

Many definitions of CHF exist,[26–29] but only selective features of this complex syndrome are highlighted. None is entirely satisfactory. A simple objective definition of CHF is currently impossible as there is no cut-off value of cardiac or ventricular dysfunction or change in flow, pressure, dimension, or volume that can be used reliably to identify patients with heart failure. The diagnosis of heart failure relies on clinical judgement based on a history, physical examination, and appropriate investigations.

For practical and operational purposes, the Task Force considers the essential components of heart failure to be a syndrome in which the patients should have the following features: symptoms of heart failure, typically breathlessness or fatigue, either at rest or during exertion, or ankle swelling and objective evidence of cardiac dysfunction at rest (*Table 1*). A clinical response to treatment directed at heart failure alone is not sufficient for diagnosis, although the patient should generally demonstrate some improvement in symptoms and/or signs in response to those treatments in which a relatively fast symptomatic improvement could be anticipated (e.g. diuretic administration). It should also be recognized that treatment may obscure a diagnosis of heart failure by relieving the patient's symptoms.

The distinctions between cardiac dysfunction, persistent heart failure, as well as heart failure that has been rendered asymptomatic by therapy and transient heart failure are outlined in *Figure 1*. It is important to note that exercise-induced ventricular dysfunction, usually caused by myocardial ischaemia, may cause a rise in ventricular filling pressure and a fall in cardiac output and induce symptoms of heart failure (e.g. breathlessness) in the absence of cardiac dysfunction at rest. However, as both the underlying pathophysiology and the treatment of this condition is generally different from that of heart failure secondary to chronic ventricular

Table 1 Definition of heart failure

I. Symptoms of heart failure (at rest or during exercise)
and
II. Objective evidence (preferably by echocardiography) of cardiac dysfunction (systolic and/or diastolic) (at rest) and (in cases where the diagnosis is in doubt)
and
III. Response to treatment directed towards heart failure

Criteria I and II should be fulfilled in all cases.

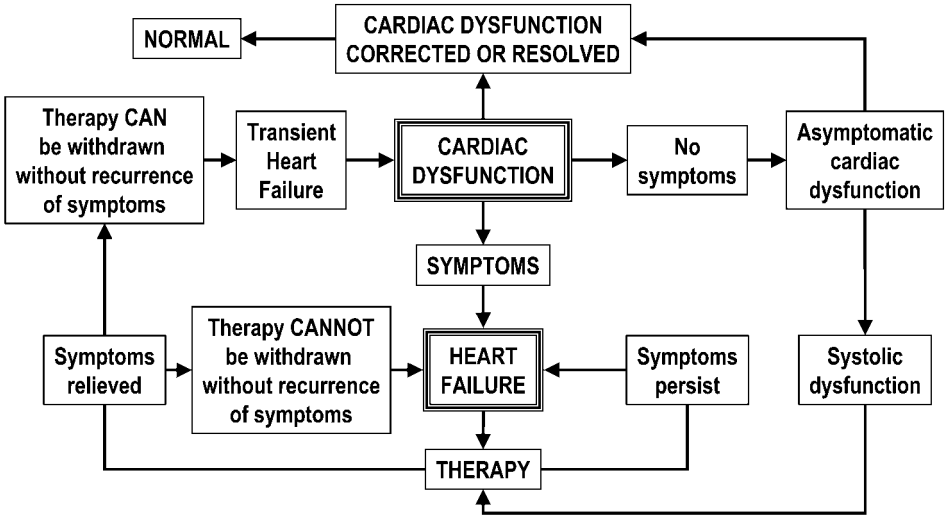

Figure 1 Relationship between cardiac dysfunction, heart failure, and heart failure rendered asymptomatic.

dysfunction, such patients should not be diagnosed as having CHF.

Asymptomatic left ventricular systolic dysfunction (ALVSD) is considered a precursor of symptomatic CHF and is itself associated with a relatively high mortality and morbidity.[30] Treatments which can improve outcome in ALVSD are available, so this condition is included in these guidelines.

Aetiology of heart failure in Europe

- Heart failure should never be the only diagnosis.

The aetiology of heart failure and the presence of exacerbating factors or other diseases that may have an important influence on management should be carefully considered in all cases. The extent to which the cause of heart failure should be pursued by further investigation will depend on the resources available and the likelihood that diagnosis will influence management.

CHF may be caused by myocardial dysfunction, valve abnormalities, pericardial disease, or it may be induced by rhythm disturbances. Acute ischaemia, anaemia, renal or thyroid dysfunction, and cardio-depressant drugs may exacerbate, or more rarely, cause heart failure. Acute pulmonary oedema and cardiogenic shock have a similar aetiological spectrum as CHF, though pulmonary oedema may be more often associated with a hypertensive crisis and normal left ventricular systolic function. Standard textbooks of cardiology should be consulted for a more extensive list of the causes of heart failure (see also *Table 23*). In Europe, myocardial dysfunction secondary to coronary artery disease, usually as a consequence of myocardial infarction, is the most common cause of heart failure among patients under the age of 75 years[31] and clear abnormalities in systolic function are usually present. Concomitant hypertension is the most important condition in this context for the development of heart failure.[32] Among elderly patients who are often less intensively investigated, an accurate diagnosis of the presence and the aetiology of heart failure is more difficult and obscured by multiple other diagnoses.[33] Systolic hypertension and cardiac hypertrophy, as well as cell loss and fibrosis may be more important causes of heart failure in the elderly and may be more likely to manifest predominantly as abnormalities of diastolic function.

Importance of identifying potentially reversible exacerbating factors

In patients with pre-existing cardiac dysfunction, symptoms of CHF may be caused or exacerbated by poor compliance to treatment, myocardial ischaemia, hypertension, tachy- or bradyarrhythmia, changes in valvular regurgitation, pulmonary embolism, aortic dissection, infection, renal dysfunction, side effects of drug therapy, and excessive fluid or sodium intake. It is important to identify any reversible factors in order to treat heart failure optimally.

Aspects of the pathophysiology of the symptoms of heart failure relevant to diagnosis

The origin of the symptoms of heart failure is not fully understood. Increased pulmonary capillary pressure is undoubtedly responsible for pulmonary oedema in part, but studies conducted during exercise in patients with CHF demonstrate only a weak relationship between capillary pressure and exercise performance.[34,35] This suggests that raised pulmonary capillary pressure is not the only factor responsible for exertional breathlessness. In this context, variation in the degree of dynamic mitral regurgitation will influence breathlessness. Abnormalities of alveolar-capillary gas diffusion, peripheral or respiratory skeletal muscle deconditioning,[36] and non-cardiac causes of dyspnoea, such as obesity or pulmonary disease, should always be considered.[37,38] Peripheral oedema is poorly related to right heart pressures: capillary permeability for fluid and small proteins may be important

additional factors. Venous insufficiency and drug therapy (calcium channel blockers) should be considered.

Although impairment of cardiac function is central to the development of heart failure, altered peripheral blood flow, especially to the kidney and skeletal muscle, is typical and probably of major pathophysiological importance.[39] Similarly, activation of a number of neuroendocrine systems is characteristic of heart failure.[40,41] Baroreceptor dysfunction is an important link between vasomotor and neuroendocrine dysfunction.[42] The understanding of CHF has moved from a haemodynamic concept into accepting the importance of neuroendocrine pathophysiological changes as important for the progression as well as the treatment of heart failure.[43] Activation of various inflammatory pathways may also contribute to cardiac dysfunction and to the clinical syndrome, particularly in more advanced stages.[44]

Possible methods for the diagnosis of heart failure in clinical practice

Symptoms and signs in the diagnosis of heart failure

- Symptoms and signs are important as they alert the observer to the possibility that heart failure exists. The clinical suspicion of heart failure must be confirmed by more objective tests particularly aimed at assessing cardiac function (*Figure 2*).

Breathlessness, ankle swelling, and fatigue are the characteristic symptoms and signs of heart failure but may be difficult to interpret, particularly in elderly patients, the obese, and in women. It should be interpreted carefully and different modes (e.g. effort and nocturnal) should be assessed.[38]

Fatigue is also an essential symptom in heart failure. The origins of fatigue are complex, including low cardiac output, peripheral hypoperfusion, as well as skeletal muscle deconditioning and confounded by difficulties in quantifying this symptom.[45] Extracardiac causes of oedema not related to heart failure are common.

Inter-observer agreement on the presence or absence of symptoms of heart failure may be low,[46] notably in the days following a myocardial infarction. There is no standard questionnaire available for the diagnosis of heart failure. In the context of clinical or epidemiological studies, several scoring systems are available that await proper validation and cannot be recommended for clinical practice at present.[47]

Peripheral oedema, raised venous pressure, and hepatomegaly are the characteristic signs of congestion of systemic veins.[48,49] Clinical signs of heart failure should be assessed in a careful clinical examination, including observing, palpating, and auscultating the patient. Unfortunately, clinical examination is often replaced by various investigations, which reduce the experience in bedside medicine among physicians. Peripheral oedema and hepatomegaly have low positive predictive value and without the determination of the jugular venous pressure may be difficult. Peripheral oedema is usually absent in well-treated heart failure and primarily left ventricular systolic dysfunction, even if severe.[49] Although cardiologists attain a high agreement on the presence of an elevated jugular venous pressure under study conditions, the reproducibility is much lower among non-specialists.[48] Moreover, many patients, even with well-documented heart failure, do not have an elevated jugular venous pressure, even if severe.[49] Tachycardia is non-specific and may be absent even in severe heart failure, particularly in the presence of beta-blocker therapy.[49] Other signs of heart failure require considerable expertise for their detection. A third heart sound is usually considered to be present in patients with severe heart failure and left ventricular systolic dysfunction,[49] but it is not specific to heart failure[50] and may be averted by medical therapy. Although cardiology specialists may attain a high agreement for the presence of a third heart sound under

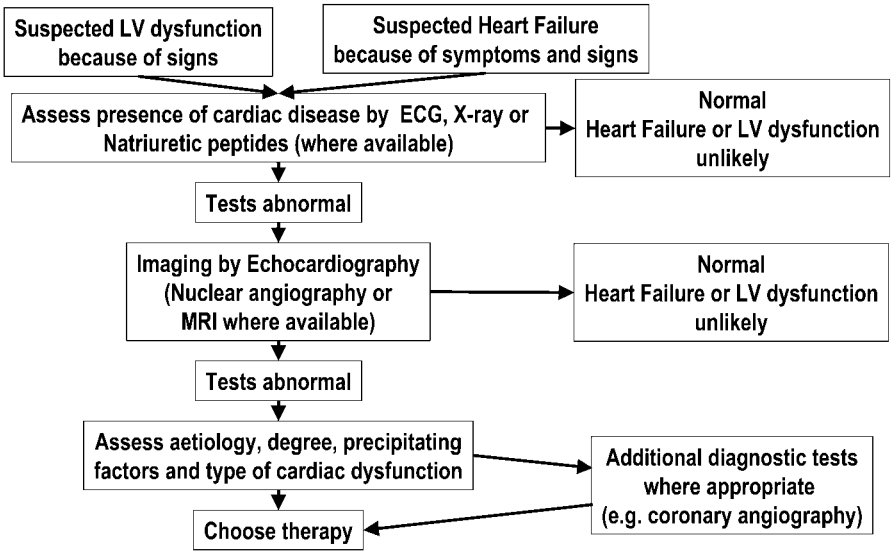

Figure 2 Algorithm for the diagnosis of heart failure or left ventricular dysfunction.

study conditions,[48] the inter-observer agreement is <50% among non-specialists[51] and probably even lower in clinical practice. Pulmonary crepitations also have low positive predictive value and inter-observer differences in eliciting this sign are notably high.[52] When cardiac murmurs are present, their origin and role in the symptomatology should be identified. In particular, mitral regurgitation is often present and may be dynamic, which would influence symptoms during exercise.

When multiple signs of heart failure are present, including a displaced apex beat, pitting oedema, a raised venous pressure, and increased P2 and when a third heart sound is heard, then in the presence of appropriate symptoms, a clinical diagnosis of heart failure may be made with some confidence. Although a clinical diagnosis reached in this way may be specific enough, it will fail to identify many patients who might benefit from treatment. The subjective component of the examination and the inability to make a permanent direct record are further weaknesses of a diagnosis made solely on the basis of clinical features.

Symptoms and the severity of heart failure

- There is a poor relationship between symptoms and the severity of cardiac dysfunction.[20,47] However, symptoms may be related to prognosis particularly if persisting after therapy.[53]

Once a diagnosis of heart failure has been established, symptoms may be used to classify the severity of heart failure and should be used to monitor the effects of therapy.[54] However, as noted subsequently, symptoms cannot guide the optimal titration of neurohormonal blockers. The New York Heart Association (NYHA) classification is in widespread use[53] (*Table 2*). The use of examples such as walking distance or number of stairs climbed is recommended. In other situations, the classification of symptoms into mild, moderate, or severe is used. Patients in NYHA class I classification would have to have objective evidence of cardiac dysfunction, have a past history of heart failure symptoms, and be receiving treatment for heart failure in order to fulfil the basic definition of heart failure.

In acute myocardial infarction, the classification described by Killip[55] to describe symptoms and signs has been used.[56] The value of questionnaires for the measurement of quality of life in the context of classification of severity is still being heavily debated. Frequently used questionnaires are the Minnesota Living with Heart Failure,[57] the SF 36,[58] and the Kansas City Cardiomyopathy Questionnaire.[59] It is important to recognize the common dissociation between symptoms and cardiac dysfunction. Symptoms are also similar in patients across different levels of ejection fraction.[60] The severity of symptoms is highly dependent on the efficacy of therapy, patient expectation, and medical interpretation. Mild symptoms should not be equated with minor cardiac dysfunction.

Table 2 New York Heart Association classification of heart failure

Class I	No limitation: ordinary physical exercise does not cause undue fatigue, dyspnoea, or palpitations
Class II	Slight limitation of physical activity: comfortable at rest but ordinary activity results in fatigue, palpitations, or dyspnoea
Class III	Marked limitation of physical activity: comfortable at rest but less than ordinary activity results in symptoms
Class IV	Unable to carry out any physical activity without discomfort: symptoms of heart failure are present even at rest with increased discomfort with any physical activity

Electrocardiogram

- A normal electrocardiogram (ECG) suggests that the diagnosis of CHF should be carefully reviewed.

Electrocardiographic changes in patients with heart failure are frequent. The negative predictive value of normal ECG to exclude left ventricular systolic dysfunction exceeds 90%.[61–63] On the other hand, the presence of anterior Q-waves and a left bundle branch block in patients with ischaemic heart disease are good predictors of a decreased ejection fraction.[19] ECG signs of left atrial overload or left ventricular hypertrophy may be associated with systolic as well as isolated diastolic dysfunction, but they have a low predictive value. A QRS width >120 ms suggests that cardiac dyssynchrony may be present and a target for treatment. The ECG is crucial for detecting atrial fibrillation or flutter, and sometimes ventricular arrhythmia, all of which are considered causative or contributing factors for heart failure. The diagnostic contribution of ECG anomalies markedly increases if clinical symptoms and signs of heart failure co-exist. ECG recordings do not need to be repeated in the absence of changes of clinical status.

The chest X-ray

- The chest X-ray should be part of the initial diagnostic work-up in heart failure.

A high predictive value of X-ray findings is only achieved by interpretation of the X-ray in the context of clinical findings and ECG anomalies.[62] The investigation is useful in detecting the presence of pulmonary congestion. Importantly, pulmonary disease contributing/causing dyspnoea can be detected.[64–67] Cardiomegaly is frequently absent not only in patients with AHF but also in cases with diastolic as well as systolic dysfunction.[68] However, in patients with CHF, an increased cardiac size, as judged by a cardiothoracic ratio >0.50, and the presence of a pulmonary venous congestion are useful indicators of abnormal cardiac function with decreased ejection fraction and/or elevated left ventricular filling pressure.[69] Pleural effusion is also common.

Interstitial and alveolar pulmonary oedema are also reliable and important signs of severe left ventricular dysfunction.[70] However, in individual patients, the radiographic findings alone do not allow a reliable estimation of the pulmonary capillary pressure and are therefore not suitable as the only basis for therapeutic decisions.[71] There may also be inter-observer variations in the interpretation of chest X-ray changes.[72,73] The relationship between radiological signs and haemodynamic findings may depend on the duration as well as the severity of cardiac dysfunction.[74]

Table 3 Modified creatinine clearance calculation

Cockroft and Gault[331]
Creatinine clearance (mL/min) = (140 − age) × weight (kg) × 1.22/S-creatinine (μmol/L)
Values should be reduced by 15% for women
The sMDRD[329]
Creatinine clearance (mL/min)/1.73 m^2 = 186.3 × $(screat)^{-1.154}$ × $(age)^{-0.203}$
For women: adjust by ×0.742 (reduction of 25%)

screat = S-creatinine in μmol/L.

Haematology and biochemistry

- The following laboratory investigations are recommended as part of a routine diagnostic evaluation of patients with CHF: complete blood count (Hb, leukocytes, and platelets), S-electrolytes, S-creatinine, S-glucose, S-hepatic enzymes, and urinanalysis. Additional tests to consider include C-reactive protein, thyroid stimulating hormone (TSH), S-uric acid, and S-urea. In acute exacerbations, it is important to exclude acute myocardial infarction by myocardial biomarkers.

Anaemia may exacerbate pre-existing heart failure and is associated with increased risk for morbidity and mortality.[75] A raised haematocrit suggests that breathlessness may be caused by pulmonary disease, cyanotic congenital heart disease, or a pulmonary arteriovenous malformation.

Elevated serum creatinine can be caused by primary renal disease, which may induce all the features of heart failure by volume overload. Heart failure and renal dysfunction often coincide because of the underlying diseases, such as diabetes and hypertension, or as a consequence of impaired kidney perfusion by reduction in cardiac output during the progression of heart failure. Treatment with diuretics and/or ACE-inhibitors sometimes together with potassium-sparing diuretics is another reason for a high S-creatinine value. Further, age alone can be a cause of reduced creatinine clearance. Calculation of creatinine clearance is given in *Table 3*. Concomitant administration of ACE-inhibitors and potassium-sparing diuretics may lead to hyperkalaemia. Untreated heart failure is rarely associated with major electrolyte disturbances, but such disturbances are quite common in patients on diuretics. Liver enzymes may be poor by hepatic perfusion.

Urine analysis is useful in detecting proteinuria and glycosuria, alerting the clinician to the possibility of underlying renal problems or diabetes mellitus, conditions that may contribute to, or complicate, heart failure. Hyponatraemia and renal dysfunction in the setting of heart failure indicate a bad prognosis.

Heart failure due to thyrotoxicosis is frequently associated with rapid atrial fibrillation, which may be the presenting feature of thyrotoxicosis in the elderly. Hypothyroidism may also present as heart failure.

Natriuretic peptides

- Plasma concentrations of certain natriuretic peptides or their precursors, especially BNP and NT-proBNP, are helpful in the diagnosis of heart failure.
- A low-normal concentration in an untreated patient makes heart failure unlikely to be the cause of symptoms.
- BNP and NT-proBNP have considerable prognostic potential though evaluation of their role in treatment monitoring remains to be determined.

Several clinical and epidemiological studies have demonstrated a direct relationship between increasing plasma concentrations of natriuretic peptides and decreasing cardiac (usually left ventricular) function.[76–78] Although this applies to atrial natriuretic peptides (ANP), 'B' type natriuretic peptide (BNP) and its precursor NT-proBNP, for which there are now commercially available assays, have been much more extensively characterized in clinical practice.

Conclusive evidence of diagnostic accuracy is now available from well-conducted clinical trials. Patients who were referred to a rapid access heart failure clinic from primary care BNP performed extremely well when compared with the gold standard diagnoses made by a panel of three cardiologists with all available clinical information. In particular, the negative predictive accuracy was 97%, i.e. to rule out the diagnosis, whereas this population with a high a priori likelihood of heart failure, the positive predictive value was also high at 70%.[15,79] Thus, the diagnostic potential of both BNP and NT-proBNP in primary care is high, a setting in which only about one-third of patients with suspected heart failure has the presence of heart failure subsequently confirmed.[80]

A large study has recently confirmed that BNP could help differentiate cardiac from respiratory acute breathlessness in the emergency room setting in the United States. The predictive accuracy of BNP for heart failure was similar to or better than other clinical variables, including the chest X-ray.[81]

Although the diagnostic potential of natriuretic peptides is less clear-cut when systolic function is normal, there is increasing evidence that their elevation can indicate that diastolic dysfunction is present.[82,83] Other common cardiac abnormalities that may cause elevated natriuretic peptide levels include left ventricular hypertrophy,

valvular heart disease, acute or chronic ischaemia, hypertension,[84] and pulmonary embolism.[85]

Although rarely, a high BNP may also signify non-cardiac disease with the most common being renal impairment.

It is important to recognize that female gender and increasing age also elevate the plasma levels, factors that must be taken into account when setting cut points.[86] It needs also to be stressed that, as with troponin measurements, these values are assay specific and not interchangeable among assays.

In considering the use of BNP and NT-proBNP as diagnostic aids, it should be emphasized that a 'normal' value cannot completely exclude cardiac disease, but a normal or low concentration in an untreated patient makes heart failure unlikely as the cause of symptoms. Nevertheless, values in the normal range are associated with an excellent prognosis and alternative causes of the symptoms should be sought in the first instance. Most importantly, it must be recognized that elevated levels are powerful predictors of death and future major cardiac events.[87] Therefore, such an observation confers 'high risk' status and mandates further cardiological investigation to elucidate the cause. In the first instance, this is likely to be an ECG, which may provide the explanation and indicate a management plan.

In clinical practice today, the place of BNP and NT-proBNP is as 'rule out' tests to exclude significant cardiac disease. Particularly in primary care but also in certain aspects of secondary care (e.g. the emergency room and clinics), the cost-effectiveness of the test suggests that a normal result should obviate the need for further cardiological tests such as in the first instance, echocardiography as well as more expensive investigations.

Echocardiography

- Echocardiography is the preferred method for the documentation of cardiac dysfunction at rest.
- The most important measurement of ventricular function is the LVEF for distinguishing patients with cardiac systolic dysfunction from patients with preserved systolic function.

The access to and use of echocardiography is encouraged for the diagnosis of heart failure. Transthoracic Doppler echocardiography (TDE) is rapid, safe, and widely available. It is a non-invasive technique that allows the assessment of chamber dimensions, wall thicknesses and geometry, indices of regional and global, systolic and diastolic ventricular function. Echocardiography also provides rapid and semi-quantitative assessment of valvular function, especially of mitral, tricuspid and aortic stenosis and regurgitation, grading of mitral regurgitation and the velocity of secondary tricuspid regurgitation for the estimate of systolic pulmonary artery pressure.

Although M-mode measurements benefit from high temporal resolution, they are inaccurate in patients with spherical ventricles and regional dysfunction. The apical biplane summation of discs method—modified Simpson's method—is validated[88] but relies on accurate endocardial definition. Although quantitative visual assessment has been shown to detect low LVEF with good sensitivity and specificity, this procedure is reliable only with experienced observers. Other measurements include fractional shortening, sphericity index, atrioventricular plane displacement,[89] myocardial performance index,[90] and left ventricular wall motion index.[91,92] The interpretation of ejection fraction with any technique shortly after an acute myocardial infarction or in the context of a mitral regurgitation is more uncertain.

Reproducibility of ejection fraction among different observers is poor, even when the same techniques are used.

Assessment of LV diastolic function

Assessment of diastolic function may be clinically useful (1) in detecting abnormalities of diastolic function in patients who present with CHF and normal LVEF, (2) in determining prognosis in heart failure patients, (3) in providing a non-invasive estimate of left ventricular diastolic pressure, and (4) in diagnosing constrictive pericarditis and restrictive cardiomyopathy.

Diagnostic criteria of diastolic dysfunction

According to recommendations from the ESC Working Group on Myocardial Function, a diagnosis of primary diastolic heart failure requires three conditions to be simultaneously satisfied: (1) presence of signs or symptoms of CHF, (2) presence of normal or only mildly abnormal left ventricular systolic function (LVEF $\geq$ 45–50%), and (3) evidence of abnormal left ventricular relaxation, diastolic distensibility, or diastolic stiffness.[4] The third criterion may be the most difficult to satisfy because of limitations in the diagnostic methods. Furthermore, it is essential to exclude pulmonary disease.[38]

The two hallmarks of left ventricular diastolic dysfunction are impaired relaxation and decreased diastolic compliance. Quantification of rate of relaxation and compliance requires invasive methods and is therefore not practical in clinical routine. Instead, different echocardiography indices of diastolic filling may be used. Importantly, these indices do not directly measure diastolic function, but serve as markers of impaired diastolic function.[93] The approaches which are most useful are the measurement of transmitral and pulmonary venous flow velocities by pulsed Doppler echocardiography[94–96] and mitral annular velocities by tissue Doppler imaging (TDI).[97] The peak early diastolic mitral flow velocity (E) is directly related to the transmitral pressure gradient and left atrial pressure and is therefore markedly load-dependent.[95,96] The peak early diastolic mitral annular velocity (E′) is less load-dependent and is related to the rate of left ventricular relaxation.[97–99]

One should also look for cardiac structural changes that may be consistent with diastolic dysfunction, in particular, left atrial enlargement and left ventricular hypertrophy.

Filling patterns and staging of diastolic dysfunction

In patients with cardiac disease, three abnormal left ventricular filling patterns have been described.[100] At an early stage of diastolic dysfunction, there is typically

a pattern of impaired myocardial relaxation with a decrease in peak transmitral E-velocity, a compensatory increase in the atrial-induced (A) velocity, and therefore a decrease in the E/A ratio.

In patients with advanced cardiac disease there may be a pattern of 'restrictive filling', with an elevated peak E-velocity, a short E-deceleration time, and a markedly increased E/A ratio. The elevated peak E-velocity is due to elevated left atrial pressure that causes an increase in the early-diastolic transmitral pressure gradient.[95] The short E-deceleration time is due to reduced left ventricular chamber compliance that leads to rapid deceleration of transmitral flow.[101,102]

In patients with an intermediate pattern between impaired relaxation and restrictive filling, the E/A ratio and the deceleration time may be normal, a so-called 'pseudonormalized filling pattern'. This pattern may be distinguished from normal filling by the demonstration of reduced peak E′-velocity by TDI[97] and by some other diagnostic approaches.[103,104]

The three filling patterns 'impaired relaxation', 'pseudonormalized filling', and 'restrictive filling' represent mild, moderate, and severe diastolic dysfunction, respectively.[97] Thus, by using the combined assessment of transmitral blood flow velocities and mitral annular velocities, it becomes possible to perform staging of diastolic dysfunction during a routine echocardiographic examination (*Figure 3*). In a given patient, however, the pattern may change over time because of changes in intrinsic myocardial function and in response to medication that modifies loading conditions. Importantly, the absolute value of E′ is dependent on the equipment that is used and instrument settings. Furthermore, transmitral velocities and mitral annular velocities are age-dependent, and any given value should be compared with age-adjusted reference values. We still lack prospective outcome studies that investigate if assessment of diastolic function by these criteria may improve management of heart failure patients.

Estimation of LV diastolic pressure

The marked sensitivity of left ventricular filling velocities to loading conditions represents a limitation when Doppler velocities are used as markers of diastolic function. The load sensitivity, however, makes it possible to estimate left ventricular diastolic pressure from the Doppler indices of filling.[105–108]

One of the most useful of these approaches is to compare the durations of antegrade transmitral flow with reversed pulmonary venous flow during atrial contraction.[98] A pulmonary venous reverse A-wave duration that exceeds transmitral A-wave duration by >30 ms is a marker of elevated LV EDP.[107] Because peak early mitral annular velocity is less preload-dependent than peak early transmitral velocity, the E/E′ ratio can be used to estimate left ventricular filling pressure.[107]

Persistence of a restrictive filling pattern of left ventricular filling after medical treatment is associated with increased mortality.[109,110]

Transoesophageal echocardiography is not recommended routinely and can only be advocated in patients who have an inadequate echo window, in complicated valvular patients, in patients with suspected dysfunction of mechanical mitral valve prosthesis, or when it is mandatory to identify or exclude a thrombus in the atrial appendage.

Repeated echocardiography can be recommended in the follow-up of patients with heart failure only when there is an important change in the clinical status suggesting significant improvement or deterioration in cardiac function.

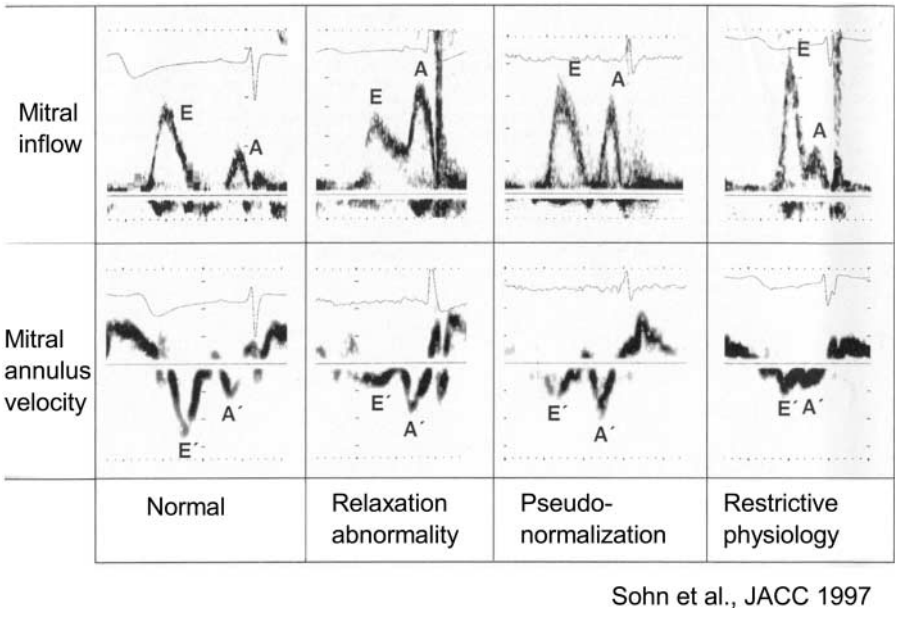

Figure 3 The three filling patterns 'impaired relaxation', 'pseudonormalized filling', and 'restrictive filling' represent mild, moderate, and severe diastolic dysfunction, respectively.[97]

Additional non-invasive tests to be considered
In patients in which echocardiography at rest has not provided enough information and in patients with coronary artery disease (e.g. severe or refractory CHF and coronary artery disease) further non-invasive imaging may include the following techniques.

Stress echocardiography
Exercise or pharmacological stress echocardiography may be useful for detecting ischaemia as a cause of reversible or persistent dysfunction and in determining the viability of akinetic myocardium.[111] Graded dobutamine infusion may be used to recruit contractile reserve.[112] Sustained contractile improvement is observed when flow reserve is appropriate, in the presence of stunning or non-transmural infarction. A biphasic response indicates that flow reserve is blunted and suggests the presence of myocardial hibernation. Although several non-controlled studies have shown that revascularization can improve regional function, clinical status, and survival in patients with a significant amount of hibernating myocardium,[113,114] a systematic assessment of myocardial viability in patients with coronary artery disease and heart failure with systolic dysfunction cannot yet be recommended.

Nuclear cardiology
Radionuclide angiography (RNA) provides reasonably accurate measurements of left and, to a lesser extent, right ventricular ejection fraction (RVEF) and cardiac volumes. Left ventricular filling dynamics can also be analysed. In none of these are the measurements reliable in the presence of atrial fibrillation. Planar myocardial scintigraphy or single photon emission computed tomography (SPECT) can be performed at rest or during stress using infusion of different agents, such as thallium[201] or 99 m technetium sestamibi. The presence and extent of ischaemia can be evaluated. Although each of these imaging modalities may have certain diagnostic and prognostic value, the routine use of nuclear cardiology cannot be recommended.

As with echocardiography, values of ejection fraction vary with the technique used. Thus, analysis using a single region of interest gives values significantly lower than when two regions are used. However, reproducibility is better than with echocardiography.

Cardiac magnetic resonance imaging

- Cardiac magnetic resonance imaging (CMR) is a versatile, highly accurate, and reproducible imaging technique for the assessment of left and right ventricular volumes, global function, regional wall motion, myocardial thickness, thickening, myocardial mass, and cardiac valves.[115,116] The method is well suited for detection of congenital defects, masses and tumours, and valvular and pericardial diseases.

Additional information can be obtained when CMR is used with paramagnetic contrast agents. Bolus injection of a gadolinium–chelate can be used to assess myocardial perfusion at rest or during pharmacological stress and, combined with regional assessment of myocardial thickening and excursion, can be used to assess myocardial ischaemia and new infarction.[117] Imaging 10–20 min after an injection of gadolinium can identify areas of delayed hyper-enhancement which are thought to reflect regions of acute infarction or chronic scar.[118] Delayed hyper-enhancement can be used to identify and distinguish full and partial-thickness scar and thus differentiate regions of contractile dysfunction due to loss of myocardium from those that are likely to reflect stunning or hibernation.[119] Marked thinning of the myocardium is also likely to reflect extensive scar.

Magnetic resonance angiography with or without paramagnetic contrast also allows imaging of many vascular beds of clinical interest (e.g. aorta, carotid, pulmonary, renal, and peripheral arteries), avoiding invasive tests and the use of potentially nephrotoxic X-ray contrast agents.

There are a few contra-indications that should be considered absolute, such as the presence of metal in the eye or brain (clips or foreign bodies) and cochlear implants. Most angioplasty stents are compatible with CMR.[120] Pacemakers, defibrillators, and other implanted medical devices have generally been considered as a contraindication to CMR but carefully selected cases have been imaged safely and effectively.[121] The major limitation of CMR for patients is claustrophobia. This may be reduced by new technologies and managing patients' anxiety.

Scan times until now have typically taken $\sim$30 min without and 60 min with an acute and delayed scan with gadolinium enhancement and pharmacological stress. New ultra-fast technologies can reduce scan times to 2–3 min.

CMR has several advantages over other imaging techniques. CMR has become the gold standard of accuracy and reproducibility against which other techniques for the assessment of volumes, mass, and wall motion should be compared.[115] There is less operator dependence when compared with echocardiography and images can be obtained when echo proves sub-optimal because of a poor acoustic window. There is better spatial resolution when compared with conventional nuclear imaging. There is no radiation or nephrotoxic contrast involved. CMR may be inferior to fast electron-beam CT techniques for the non-invasive assessment of coronary arteries. However, CMR is expensive, a relatively rare resource and, in terms of practical management of most patients with heart failure, it has not been shown to be superior to echocardiography.

Pulmonary function

- Measurements of lung function are of little value in diagnosing CHF. However, they are useful in excluding respiratory causes of breathlessness. Spirometry can be useful to evaluate the extent of obstructive airways disease, which is a common comorbidity in patients with heart failure.

Epidemiological studies suggest a strong association between chronic obstructive airways disease and ischaemic heart disease, one of the principal causes of heart failure.[122] Peak expiratory flow rate (PEFR) and forced expiratory volume in 1s (FEV_1) are reduced by CHF but not to the same extent as in symptomatic obstructive airways disease.[123] Alveolar-capillary gas-diffusing capacity is related to exercise capacity, which can provide prognostic information.[124,125] Other variables have no value in diagnosing or in grading disease progression in patients with CHF.[126]

Dyspnoea and fatigue are the two main causes of exercise limitation in patients with CHF. Respiratory muscle dysfunction may also play an important role.[127]

Exercise testing

- In clinical practice, exercise testing is of limited value for the diagnosis of heart failure. However, a normal maximal exercise test in a patient not receiving treatment for heart failure excludes heart failure as a diagnosis. The main applications of exercise testing in CHF are focused more on functional and treatment assessment and on prognostic stratification.

Recommendations for exercise testing in heart failure patients have been released by the Working Group on Cardiac Rehabilitation and Exercise Physiology and the Working Group on Heart Failure of the ESC.[128]

In recent years, exercise testing has been used for prognostic purposes and exercise capacity with on-line gas exchange measurements has proved to be an important component of the risk profile in CHF. A peak VO_2 $<$10 mL/kg per min identifies high risk and a peak VO_2 $>$18 mL/kg per min identifies low risk patients. Values between these cut-off limits define a 'grey' zone of medium risk patients without further possible stratification by VO_2. The available prognostic data for women are inadequate. Assessment of the ventilatory response to exercise, measured as the slope of the relation between minute ventilation and carbon dioxide production during exercise, has been shown to have an independent prognostic value in CHF. Its prognostic value has been superior to that of peak VO_2 in recent studies.[129] To date, there have been no reports of serious problems related to exercise testing in CHF.[128] The 6 min walk test has been widely implemented in clinical trials.[130,131] The 6 min walk test may provide useful prognostic information when walking distance is $<$300 m. However, for use in the clinical setting, the value of the 6 min walk test is unclear.

Invasive investigation

- Invasive investigation is generally not required to establish the presence of CHF but may be important in elucidating the cause or to obtain prognostic information.

Three diagnostic tools may be helpful in different situations: coronary angiography, haemodynamic monitoring, and endomyocardial biopsy. None of them is indicated as a routine procedure.

Cardiac catheterization

Coronary angiography should be considered in patients with acute or acutely decompensated CHF and in patients with severe heart failure (shock or acute pulmonary oedema) who are not responding to initial treatment. Coronary angiography should also be considered in patients with angina pectoris or any other evidence of myocardial ischaemia if they are not responding to appropriate anti-ischaemic treatment. However, revascularization of hibernating or ischaemic myocardium in heart failure has not been shown to improve outcome in controlled trials.[132] Angiography can be used to exclude coronary artery disease when a diagnosis of idiopathic dilated cardiomyopathy is considered. Coronary angiography is also indicated in patients with refractory heart failure of unknown aetiology and in patients with evidence of severe mitral regurgitation or aortic valve disease.

Monitoring of haemodynamic variables by means of a pulmonary arterial catheter is indicated in patients who are hospitalized for cardiogenic shock or to direct treatment of patients with CHF not responding promptly to initial and appropriate treatment.[21] Routine right heart catheterization should not be used to tailor chronic therapy.

Endomyocardial biopsy may be useful in selected patients with unexplained (myocardial ischaemia excluded) heart failure. Furthermore, biopsy may help to differentiate between constrictive and restrictive aetiologies.

Tests of neuroendocrine evaluations other than natriuretic peptides

- Tests of neuroendocrine activation are not recommended for diagnostic or prognostic purposes in individual patients.

Although there are no doubts about the importance of neuroendocrine mechanisms in the pathogenesis of heart failure, the role of neuroendocrine factors in the diagnosis is less clear. In large cohorts of patients there is good evidence that circulating levels of noradrenaline, renin, angiotensin II, aldosterone, vasopressin, endothelin-1, and adrenomedullin are related to the severity and prognosis of heart failure, but in individual patients these predictors are inaccurate and difficult to interpret. Diuretics, vasodilator agents, ACE-inhibitors, and beta-blockers alter plasma concentrations of neuroendocrine substances in a complex fashion which limits diagnostic use. Plasma noradrenaline increases with age and healthy subjects over the age of 75 years may have plasma concentrations of noradrenaline in the heart failure range.[133]

Holter electrocardiography: ambulatory ECG, and long-time ECG recording

- Conventional Holter monitoring is of no value in the diagnosis of CHF, though it may detect and quantify the nature, frequency, and duration of atrial and ventricular arrhythmias which could be causing or exacerbating symptoms of heart failure. Long-time

ECG recording (LTER) should be restricted to patients with CHF and symptoms suggestive of an arrhythmia.

The high prevalence of ventricular ectopy and ventricular tachycardia is well recognized, but it remains unclear whether ventricular arrhythmias identify patients at high risk of sudden death. In the GESICA trial, patients with non-sustained ventricular tachycardia were found to have significantly more severe heart failure, a higher overall mortality and a greater incidence of sudden death.[134] However, multivariate analysis of CHF-STAT and PROMISE studies supports that ventricular arrhythmias are non-specific predictors of mortality. Thus, ambulatory electrocardiographic monitoring alone seems not to provide additional prognostic information.[135] Furthermore, the finding of asymptomatic non-sustained ventricular arrhythmias on LTER does not identify specific candidates for anti-arrhythmic or device therapy.

Heart rate variability

Heart rate variability (HRV) is a marker of autonomic balance, a balance that is characterized by an increased sympathetic activation and reduced vagal stimulation in patients with heart failure. The diagnostic and prognostic utility of this observation has been extensively investigated.[136–138] A correlation between time and frequency domain HRV measures and clinical and haemodynamic variables exists,[139,140] and time domain variables can predict survival independently from clinical and haemodynamic data.[135,136,141,142] The value of this technology in clinical practice, however, still remains to be determined.

Requirements for the diagnosis of heart failure in clinical practice

- To satisfy the definition of heart failure, symptoms of heart failure and objective evidence of cardiac dysfunction must be present (*Table 1*). The assessment of cardiac function by clinical criteria alone is unsatisfactory. Cardiac dysfunction should be assessed objectively.

The echocardiogram is the single most effective tool in widespread clinical use. Other conditions may mimic or exacerbate the symptoms and signs of heart failure and therefore need to be excluded (*Table 4*). An approach (*Figure 2*) to the diagnosis of heart failure in symptomatic patients should be performed routinely in patients with suspected heart failure in order to establish the diagnosis. Additional tests (*Table 5*) should be performed or re-evaluated in cases in which diagnostic doubt persists or clinical features suggest a reversible cause for heart failure. Coronary artery disease is a common, and probably underdiagnosed, cause of heart failure. If there is reason to believe that the patient will benefit from revascularization, then an angiogram and additional tests as appropriate should be done.

Figure 2 represents a simplified plan for the evaluation of a patient presenting with symptoms suggestive of heart failure or signs giving suspicion of left ventricular systolic dysfunction. *Table 6* provides a management outline connecting the diagnosis component of the guidelines with the treatment section.

The symptoms are similar in heart failure because of systolic and diastolic dysfunction.[60,143] Accordingly, the same criteria should be used for the diagnosis of both conditions with the application of the assessment of LV myocardial function as described previously.

Prognostication

Prognosis

- The problem of defining prognosis in heart failure is complex for many reasons: several aetiologies, frequent comorbidities, limited ability to explore the paracrine pathophysiological systems, varying individual

Table 4 Assessments to be performed routinely to establish the presence and likely cause of heart failure

Assessments	Diagnosis of heart failure			Suggests alternative or additional diagnosis
	Necessary for	Supports	Opposes	
Appropriate symptoms	+++		+++ (If absent)	
Appropriate signs		+++	+ (If absent)	
Cardiac dysfunction on imaging (usually echocardiography)	+++		+++ (If absent)	
Response of symptoms or signs to therapy		+++	+++ (If absent)	
ECG			+++ (If normal)	
Chest X-ray		If pulmonary congestion or cardiomegaly	+ (If normal)	Pulmonary disease
Full blood count				Anaemia/secondary polycythaemia
Biochemistry and urinalysis				Renal or hepatic disease/diabetes
Plasma concentration of natriuretic peptides in untreated patients (where available)		+ (If elevated)	+++ (If normal)	Can be normal in treated patients

+ = of some importance; +++ = of great importance.

Table 5 Additional tests to be considered to support the diagnosis or to suggest alternative diagnoses

Tests	Diagnosis of heart failure		Suggests alternative or additional diagnoses
	Supports	Opposes	
Exercise test	+ (If impaired)	+++ (If normal)	
Pulmonary function tests			Pulmonary disease
Thyroid function tests			Thyroid disease
Invasive investigation and angiography			Coronary artery disease, ischaemia
Cardiac output	+++ (If depressed at rest)	+++ (If normal; especially during exercise)	
Left atrial pressure (pulmonary capillary wedge pressure)	+++ (If elevated at rest)	+++ (If normal; in absence of therapy)	

+ = of some importance; +++ = of great importance.

progression and outcome (sudden vs. progressive heart failure death), and efficacy of treatments. Moreover, several methodological limitations weaken many prognostic studies. The variables more consistently indicated as independent outcome predictors are reported in *Table 7*

The imprecision in making the diagnosis of CHF does not help in defining the prognosis of this syndrome. The problem has become more complex since the recognition of heart failure with a preserved left ventricular systolic function.[144] Considering that a correct diagnosis of heart failure required evidence of left ventricular systolic dysfunction—in practice a low ejection fraction—prognostic stratification needs to be re-considered. However, prognostic analyses have been predominantly carried out on populations enrolled in trials and because an enrolment criterion in most trials published so far has been a reduced LVEF, there are few data on which to base a stratification analysis of heart failure with preserved systolic function.[145] For this reason, what can be said thus far concerns mainly patients with proven left ventricular systolic dysfunction.

Our ability to explore the functional alterations of many biological systems is limited by the available access to the body investigation which, apart from the imaging techniques, is the blood. This precludes from the analysis all short-living paracrine mediators which do not enter the circulation or pass into the blood in small amounts not representing the level of activity of the specific function that they mediate.

Although heart failure is a chronic syndrome, it does not evolve gradually. Periods of relative stability alternate with acute destabilizations. The prognostic stratification should, therefore, be different in relation to the goal. Stratification during an acute unstable phase should have a short-term aim and should guide immediate decisions. Stratification during a stable phase could have a long-term aim and should predict and, hopefully help to prevent, destabilizations and death in the mid-term and long-term. Moreover, the activation of the biological systems involved in the pathophysiology of heart failure can occur at different times during the course of the syndrome. Consequently, the prognostic significance of several variables can change according to the evolutionary stage of the disease.

Table 6 Management outline

Establish that the patient has heart failure (in accordance with the definition presented on page 3, Diagnosis section)
Ascertain presenting features: pulmonary oedema, exertional breathlessness, fatigue, peripheral oedema
Assess severity of symptoms
Determine aetiology of heart failure
Identify precipitating and exacerbating factors
Identify concomitant diseases relevant to heart failure and its management
Estimate prognosis based on page 13
Assess complicating factors (e.g. renal dysfunction, arthritis)
Counsel patient and relatives
Choose appropriate management
Monitor progress and manage accordingly

About half of all deaths from heart failure are sudden, frequently, but not always, of an arrhythmic origin.[147] Sudden death may occur at any stage of the syndrome in patients with very different conventional risk profiles.

Introduction of new treatments can modify the prognostic weight of the same variable over time. For example, beta-blockers influence left ventricular function more than exercise capacity.[148,149] Thus, the predictive power of these two factors can differ in patients treated or not treated with beta-blockers.[150]

Relatively weak prognostic power of many variables is also explained by a series of methodological flaws. These include small, selected samples, short duration of follow-ups, spot (non-sequential) determination of the potential indicators, few and selected variables included in the multivariate analyses which should (but do not) produce 'independent' prognostic indicators.

Table 7 Risk stratification in CHF predictors

Demographic and historical	Clinical	Electrophysiologic	Functional/exertional	Blood	Central haemodynamic
Advanced age*[159,332,333]	High heart rate[346]	Broad QRS[297,335]	VO_2 max* (mL/kg per min $<10-14$)[128,168,169]	High serum BNP*[84,336]	Low LVEF*[155,332,337,338]
Coronary aetiology[146,159]	Persistent low BP*[159]	Low heart rate variability[339,340]	High VE/VCO_2 ratio[170]	High serum norepinephrine[341,342]	Increased left ventricular volumes[157,158]
Diabetes[343]	NYHA functional Class III–IV*[145,159,332]	Complex ventricular rhythms[315,341]	Low 6 min walking ability[131,344]	Low serum sodium*[159,165]	Low cardiac index[159]
Resuscitated sudden death*[315]	Involuntary weight loss[345]	T-wave alternans[338]		High serum creatinine*[159,164,165]	High left ventricular filling pressure[159,332]
Race[334]	Ventilatory rhythm and rate disturbances[347,348]			High serum bilirubine*[165]	Restrictive mitral filling pattern[162,349]
				Anaemia[350]	Impaired right ventricular function*[160,161]
				High serum troponin[351]	Cardiothoracic ratio[68,341]
				High serum uric acid[352]	

CHF = chronic heart failure; BP = blood pressure; NYHA = New York Heart Association; VE = ventilation volume per min; VCO_2 = ventilation of CO_2; BNP = brain natriuretic peptide; LVEF = left ventricular ejection fraction.
*Strong.

Numerous prognostic algorithms have been reported. Usually the independent prognostic predictors considered are clinical variables, chest X-rays, ECG, and echocardiographic parameters. Indicators that can only be measured with sophisticated techniques and/or invasive methods can only be recommended in specific situations in which they have been demonstrated to be of important benefit in making decisions concerning the use of life-saving drugs or devices or submission to demanding therapeutic strategies such as heart transplantation. Excellent reviews of the prognostic value of different variables and algorithms in heart failure have been published.[151–154]

Prognostic stratification must be useful for making therapeutic decisions. For example, several studies have clearly demonstrated that in asymptomatic patients with left ventricular dysfunction ejection fraction is an important prognostic marker for the development of manifest heart failure and death.[155,156] Similarly, volume changes over time[157] and the onset or worsening of mitral regurgitation[158] have important decisional implications because they should lead to further diagnostic investigations and/or intensification of therapy. In contrast, with the exception of brain natriuretic peptide, degree of neurohormonal activation cannot guide the initiation of treatment with ACE-inhibitors or beta-blockers.

Both neurohormonal activation and left ventricular systolic dysfunction tend to fall into a uniformly reduced range in advanced heart failure, such that their incremental value in prognostic stratification tends to decrease as the heart failure worsens.[159] In contrast, central haemodynamic patterns and right ventricular function take on prognostic importance in severe heart failure.[160–163] If right ventricular function deteriorates, the clinical situation can dramatically worsen and alternative treatments (e.g. transplantation) should be considered. The predictive importance of haemodynamic data is greatest when the data are collected after therapy maximization: in this way the haemodynamic indicator is linked to two other indicators, namely, current therapy and exhausted response to therapy.[159,160] This is also true for other functional parameters whose relevance lies not so much in an absolute value, but in a capacity to change following acute interventions and chronic therapy.[162]

When making decisions, parameters indicating organ damage such as elevated blood levels of creatinine,[159,164] bilirubine,[165] neurohormonal activation and hyponatremia[159,165] acquire relevance in advanced heart failure that they do not have in mild to moderate failure. In the last few years, renal dysfunction has emerged as one of the most potent risk markers in heart failure, with a predictive value not lesser than the degree of left ventricular dysfunction.[159,164,166] Similarly, pulmonary resistance is of considerable significance (though only in a restricted subset of patients) when it must be decided whether to use ventricular assistance or replacement therapies.[167]

A markedly reduced exercise capacity in optimized therapy is a parameter traditionally used in heart

failure as an indicator of irreversible cardiovascular compromise and as an indication for heart transplant.[128,168] However, the subjective components of both the doctor and the patient in deciding to interrupt the exercise may make the exercise capacity sometimes uncertain.[169] Other exercise parameters seem complementarily valuable, in particular the VE/VCO2 slope, which appears more objective and physiologically comprehensive. It includes a measure of the effects of musculoskeletal dysfunction on the central nervous system and was proven to be an excellent prognostic marker.[170]

New validated information and more integrated approaches may offer, in the future, prognostic algorithms that are more robust for prognostication in heart failure. Genomics and proteomics may offer novel disease markers and risk (or protecting) factors. However, to date, no tests can overcome the clinical judgement in grading risk and guiding therapy in heart failure patients.

Treatment of heart failure

Introduction

Throughout the past 10–15 years, the therapeutic approach to heart failure has undergone considerable change. Current treatment not only concerns symptomatic improvement, but also increasingly focuses on preventing the transition of asymptomatic cardiac dysfunction to symptomatic heart failure, preventing worsening of symptoms/functional limitations of heart failure and reducing mortality. As this is likely to be a slow process, the effects of novel preventive therapies may, in contrast to the often more rapid effects of pure symptomatic treatment, only become apparent after time.

Thus, short- and long-term objectives with individualized therapies should be identified. In addition to improvements in symptoms, well-being (quality of life) and survival, important treatment targets include cardiac remodelling, neuroendocrine activation, fluid retention, and renal dysfunction. Accordingly, because heart failure is a complex syndrome, the therapeutic approaches may need several strategies in combination to target different mechanisms.

However, as the therapeutic approaches to heart failure are multiple, including general measures, pharmacological therapy, mechanical devices and surgical interventions, they will not always be applicable in each patient. Adverse effects and interaction between different forms of treatment may preclude their use in some. Moreover, rapid deterioration of the clinical condition can require modification of the therapeutic approach.

There are regional differences in the approach to heart failure treatment in Europe. These differences are attributable to variations in aetiology and in health resources. Of more importance, perception and acceptance of the usefulness and need to prescribe therapies proven to be effective in large controlled trials by the different physicians taking care of heart failure patients are slow. Continuous education is clearly needed.

Aims of treatment in heart failure

The aims of heart failure management are those of the treatment of any disease in general and consist of several components (*Table 8*).

Prevention of heart failure

- The development of heart failure may be delayed or prevented by early management of conditions leading to heart failure, in particular in high risk patients with hypertension and/or coronary artery disease (Class of recommendation I, level of evidence A).

The prevention of heart failure should always be a primary objective. Many potential causes of myocardial damage can be treated and the extent of myocardial damage reduced. Examples include management of risk factors for coronary heart disease, treatment of ischaemia, early triage of acute myocardial infarction, prevention of reinfarction, accurate identification, and aggressive treatment of hypertension and some causes of specific heart muscle disease, timely correction of valve disorders, and congenital heart disease.

Population-based studies clearly demonstrate that hypertension is a major risk factor for CHF and contributes a large proportion of heart failure patients, suggesting that early and aggressive blood pressure control is a promising strategy for preventing CHF.[32,171] These epidemiologic studies also point to coronary heart disease as a major contributor to the development of CHF particularly in men.[171,172]

In hypertension, angiotensin-converting enzyme inhibitors (ACE-inhibitors), angiotensin receptor blockers or a combination of diuretics/beta-blockers, reduces the incidence of heart failure death or hospital admissions for heart failure.[173] In ALLHAT doxazosin was associated with a significant increase in heart failure compared with chlortalidone.[174] Furthermore, chlortalidone was associated with a lower incidence of heart failure when compared with lisinopril or amlodipine. The applicability of ALLHAT to the European population remains, however, debated as this trial enrolled a substantial proportion of Afro-Americans.

Several randomized trials indicate that early intervention with ACE-inhibitors or angiotensin receptor antagonists reduces significantly the occurrence of heart failure

Table 8 Aims of treatment

Prevention
Prevention and/or controlling of diseases leading to cardiac dysfunction and heart failure
Prevention of progression to heart failure once cardiac dysfunction is established
Morbidity
Maintenance or improvement in quality of life
Avoid re-admissions
Mortality
Increased duration of life

in high cardiovascular risk populations such as patients with previous cardiovascular disease, diabetes, alone or with nephropathy, and hypertension,[175–179] In populations at high cardiovascular risk, statin or antiplatelet therapy with clopidogrel have shown a reduction in the development of heart failure.[180,181]

When myocardial dysfunction is already present, the first objective is to remove the underlying cause of ventricular dysfunction if possible (e.g. ischaemia, toxic substances, alcohol, drugs, and thyroid disease). The second objective of modern therapy is to modulate progression from asymptomatic left ventricular dysfunction to heart failure.

How to modulate progression from asymptomatic left ventricular dysfunction to heart failure is described on page 32, Treatment of Asymptomatic Left Ventricular Dysfunction.

Management of CHF

In CHF that is caused by systolic cardiac dysfunction the therapeutic approach consists of general advice and other non-pharmacological measures, pharmacological therapy, mechanical devices, and surgery. The currently available types of management are outlined in *Table 9*.

The approach to the treatment of specific patient subgroups, i.e. the elderly or heart failure that is caused by predominant diastolic dysfunction, is addressed in special sections of these guidelines. The treatment of AHF, pulmonary oedema, and cardiogenic shock has been presented in a separate document.[21]

Non-pharmacological management

General advice and measures

(Class of recommendation I, level of evidence C for non-pharmacological management unless stated otherwise.)

Educating patients and family

Patients with CHF and their close relatives should receive general advice (*Table 10*).

Weight monitoring

Patients are advised to weigh themselves on a regular basis to monitor weight gain (preferably as part of a regular daily routine, for instance after morning toilet) and, in case of a sudden unexpected weight gain of >2 kg in 3 days, to alert a health care provider or adjust their diuretic dose accordingly (e.g. to increase the dose if a sustained increase is noted).

Dietary measures

Sodium. Controlling the amount of salt in the diet is a problem that is more relevant in advanced than in mild heart failure. Salt substitutes must be used with caution as they may contain potassium. In large quantities, in combination with an ACE-inhibitor, they may lead to hyperkalaemia.[182]

Table 9 General advice and measures, exercise, pharmacological therapy, and devices and surgery

Non-pharmacological management
General advice and measures
Exercise training
Pharmacological therapy
ACE-inhibitors
Diuretics
Beta-adrenoceptor antagonists
Aldosterone receptor antagonists
Angiotensin receptor antagonists
Cardiac glycosides
Vasodilator agents (nitrates/hydralazine)
Positive inotropic agents
Anti-coagulation
Anti-arrhythmic agents
Oxygen
Devices and surgery
Revascularization (catheter interventions and/or surgery),
Other forms of surgery (mitral valve repair)
Bi-ventricular pacing (resynchronization therapy)
ICD
Heart transplantation, ventricular assist devices, artificial heart
Ultrafiltration, haemodialysis

Fluids. Instructions on fluid control should be given to patients with advanced heart failure, with or without hyponatraemia. However, the exact amount of fluid restriction remains unclear. In practice, a fluid restriction of 1.5–2 L/day is advised in advanced heart failure.

Alcohol. Moderate alcohol intake (one beer or 1–2 glasses a wine/day) is permitted. Alcohol consumption must be prohibited in suspected cases of alcoholic cardiomyopathy.

Obesity

Treatment of CHF should include weight reduction in obese patients. The patient is overweight if his/her body mass index (BMI) (i.e. the actual weight in kilograms divided by height in metres squared) lies between 25 and 30, and obese if it is >30.

Abnormal weight loss

Clinical or sub-clinical malnutrition is present in $\sim$50% of patients with severe CHF.[6] The wasting of total body fat and lean body mass that accompanies weight loss is called cardiac cachexia.[183] Cardiac cachexia is an important predictor of reduced survival.[184]

Consider the possibility of abnormal weight loss when:

(i) a body weight $<90\%$ of ideal body weight or
(ii) a documented non-intentional weight loss of ≥ 5 kg or $\geq 7.5\%$ of the previous normal non-oedematous weight in the previous 6 months and/or
(iii) BMI (weight/height^2) < 22 kg/m^2.

The aim of treatment is to achieve an increase in non-oedematous body weight, preferably by increasing

Table 10 List of subjects to discuss with a heart failure patient and his family

General advice
Explain what heart failure is and why symptoms occur
Causes of heart failure
How to recognize symptoms
What to do if symptoms occur
Self-weighing
Rationale for treatments
Importance of adhering to pharmacological and non-pharmacological prescriptions
Refrain from smoking
Prognosis
Drug counselling
Effects
Dose and time of administration
Side effects and adverse affects
Signs of intoxication
What to do in case of skipped doses
Self-management
Rest and exercise
Rest
Exercise and activities related to work
Daily physical activity
Sexual activity
Rehabilitation
Vaccinations
Travel
Dietary and social habits
Control sodium intake when necessary, e.g. some patients with severe heart failure
Avoid excessive fluids in severe heart failure
Avoid excessive alcohol intake

muscle mass through adequate physical exercise. Small, frequent meals are indicated when reduced food intake results from nausea, dyspnoea, or a feeling of bloatedness.

Smoking
Smoking should always be discouraged. The use of smoking cessation aids should be actively encouraged and may include nicotine replacement therapies.

Travelling
High altitudes, very hot or humid places should be discouraged. In general, short air flights are preferable to long journeys by other means of transport. In patients with severe heart failure, long air flights can cause problems (e.g. dehydration, excessive limb oedema, and deep venous thrombosis) and patients should be cautioned. It is also worth discussing potential effects of changes in diet during journeys and actions in cases of acute gastro-enteritis. The use of diuretics and vasodilators may have to be adapted in case of excessive sodium and fluid loss in hot, humid climates.

Sexual activity
It is not possible to dictate guidelines about sexual activity counselling. Recommendations are given to reassure the not severely compromised, but frightened patient, to reassure the partner who is often even more frightened, and perhaps refer the couple for specialist counselling. If appropriate, advise the use of sublingual nitrates before sexual activity and discourage major emotional involvements. PDE5-inhibitors are not recommended in advanced heart failure. If used, it should be avoided within 24–48 h of nitrate intake depending on agent. Patients in the NYHA class II are at intermediate risk and patients in class III–IV are at high risk of cardiac decompensation triggered by sexual activity.[185] Little is know about the effects of treatments for heart failure on sexual function.

Advice on immunizations
There is no documented evidence of the effects of immunization in patients with heart failure. Pneumococcal and influenza immunization may reduce the incidence of respiratory infections that may worsen heart failure. Immunization for influenza is widely used.

Drug counseling
Self-management (when practical) of the dose of the diuretic, based on changes in symptoms and fluid balance, should be encouraged. Within pre-specified and individualized limits, patients are able to adjust their diuretics.

Desired effects and side effects of all drugs should be thoroughly explained. Increased patient involvement (concordance) in chronic disease should be the background for the counselling. With this in mind, the following information on drugs could be provided: improvement may be gradual and only complete after several weeks and with some drugs months of treatment; the need for gradual titration with ACE-inhibitors, angiotensin receptor blockers, and beta-blocking drugs to a desired dosage level, which will not directly improve the patient's symptoms; in case dehydration occurs (diarrhoea, profuse sweating in hot climates) to reduce the dose of diuretics; how to act if symptomatic hypotension occurs (reduction of the diuretic and, if necessary, temporary reduction of the dose of the ACE-inhibitor, angiotensin receptor blocker, or beta-blocker); that coughing might occur with the use of ACE-inhibitors as well as an alteration in taste; to avoid non-steroidal inflammatory agents (including coxibs) in combination with ACE-inhibitors (remark over the counter access); possible use of nitrates, in sublingual or spray form, as a transitory symptomatic treatment, administered at the onset of acute dyspnoea or as prevention in certain situations.

Drugs to avoid or beware
The following drugs should be used with caution when co-prescribed with any form of heart failure treatment or avoided:[186]

(i) Non-steroidal anti-inflammatory drugs (NSAIDS) and coxibs
(ii) Class I anti-arrhythmics (page 28)
(iii) Calcium antagonists (verapamil, diltiazem, short-acting dihydropyridine derivatives (page 27)
(iv) Tricyclic anti-depressants
(v) Corticosteroids
(vi) Lithium.

Rest, exercise, and exercise training

Rest

In AHF or destabilization of CHF physical rest or bed rest is necessary. Passive mobilization exercises are carried out to prevent untoward effects resulting from prolonged bed rest and to attenuate the risk of venous thrombosis. As the clinical condition of the patient improves, respiratory exercises and active mobilization can be carried out.

Exercise

In order to prevent muscle de-conditioning the patient, if in a stable condition, should be encouraged to and advised on how to carry out daily physical and leisure time activities that do not induce symptoms. Strenuous or isometric exercises and competitive and tiring sport should be discouraged. If the patient is employed, their work tasks must be assessed and advice given on whether they can be continued.

Exercise training

Exercise training programs are encouraged in stable patients in NYHA class II–III. In clinical practice, exercise intolerance in CHF has a multi-factorial aetiology. Changes in the periphery rather than left ventricular performance itself are important determinants of exercise capacity. Several small clinical and mechanistic studies and some randomized trials have shown that regular exercise can safely increase physical capacity by 15–25%, improve symptoms and perception of quality of life in patients with stable class II and III heart failure[187] (Class of recommendation I, level of evidence B). No significant deleterious effects or significant deterioration in central haemodynamics have been reported with exercise training.

Standardized recommendations for exercise training in heart failure patients by the ESC have been published.[128]

Exercise training can be performed by either interval or steady state exercise, applying intensities of 60–80% of the predetermined peak heart rate. Interval training methods may allow for more intense exercise stimuli on peripheral muscles than obtained during steady-state training, but without inducing greater cardiovascular stress. Titration of exercise training should be performed in the following order: duration, then frequency, and then intensity. Details are provided in *Table 11*.

Pharmacological therapy

Angiotensin-converting enzyme inhibitors

- ACE-inhibitors are recommended as first-line therapy in all patients, with or without symptoms, who have reduced LVEF expressed as a reduced LVEF, i.e. $<$40–45% to improve survival, symptoms, functional capacity, and reduction of hospitalizations (Class of recommendation I, level of evidence A).
- ACE-inhibitors should be given as the initial therapy in the absence of fluid retention. In patients with fluid retention ACE-inhibitors should be given together with diuretics (Class of recommendation I, level of evidence B).
- ACE-inhibition should be initiated in patients with signs or symptoms of heart failure, even if transient, after the acute phase of myocardial infarction, even if the symptoms are transient to improve survival, reduce reinfarctions and hospitalizations for heart failure (Class of recommendation I, level of evidence A)
- ACE-inhibitors should be uptitrated if possible to the dosages shown to be effective in the large, controlled trials in heart failure (Class of recommendation I, level of evidence A), and not titrated based on symptomatic improvement alone (Class of recommendation I, level of evidence C).

ACE-inhibitors in asymptomatic left ventricular dysfunction

Asymptomatic patients with a documented left ventricular systolic dysfunction benefit from long-term ACE inhibitor therapy (Class of recommendation I, level of evidence A). The consistency of data from the SOLVD Prevention Study, Survival and Ventricular Enlargement (SAVE) and TRACE has shown that asymptomatic patients with left ventricular dysfunction will have less development of symptomatic heart failure and hospitalizations for heart failure.[14,188–190]

ACE-inhibitors in symptomatic heart failure

A meta-analysis in 12 763 patients with left ventricular dysfunction and/or heart failure from five large controlled trials, including three studies in patients early after myocardial infarction, showed that ACE-inhibition significantly reduces mortality, admissions for heart failure and re-infarction, independent of age, sex and baseline use of diuretics, and aspirin and beta-blockade. Benefit was apparent over the full range of left ventricular function at baseline.[191]

The absolute benefit is greatest in patients with most severe heart failure.[192] ACE-inhibition markedly enhances survival in patients with signs or symptoms of heart failure after the acute phase of myocardial infarction, even if the symptoms are transient.[193] In addition to these effects on mortality, ACE-inhibitors in general improve the functional status of patients with heart failure. In contrast, only small benefits in exercise capacity occur.

ACE-inhibitors should always be uptitrated to the target dose used in large controlled clinical trials, if tolerated, to reduce long-term morbidity and mortality. ACE-inhibitors should not be titrated based on symptomatic improvement.

Important adverse effects associated with ACE-inhibitors are cough, hypotension, renal insufficiency, hyperkalaemia, angioedema, and syncope. Although cough may often be due to heart failure or concomitant diseases (e.g. respiratory disease), dry cough is a side effect of ACE-inhibitors. Severe cough may lead to discontinuation of ACE-inhibitor therapy. Some patients may tolerate re-institution of the ACE-inhibitor after a drug-free period. The substitute for ACE-inhibitors

Table 11 Exercise training

Steady state training
Frequency of sessions
Shorter multiple daily sessions of 5–10 min should be advised to more compromised patients; longer (20–30 min) sessions 3–5 times a week should be recommended to patients with good functional capacity
Intensity of training sessions
Initial improvements of aerobic capacity and symptoms in traditional programmes occur at 4 weeks; the maximum time required to attain peak responses in physical and cardiopulmonary variables is 16 and 26 weeks, respectively; then responses plateau. Three stages of progression have been observed: an initial stage, improvement, and maintenance stage
In the initial stage, intensity should be kept at a low level (e.g. 40–50% peak VO_2), increasing the exercise duration from 5 to 15 min. Exercise duration and frequency of training are increased according to symptoms and clinical status
During the improvement stage, the gradual increase of intensity (50% → 60% → 70% and even → 80%, if tolerated, of peak VO_2) is the primary aim; prolongation of a session to 15–20 min, and if tolerated, up to 30 min is a secondary goal
The maintenance stage in exercise programmes usually begins after the first 6 months of training. Further improvements may be minimal, but continuing the exercise training is important. Effects of a 3 week residential training programme were lost after only 3 weeks of activity restriction, suggesting the need for implementing long-term exercise training into the therapy management of CHF
Interval training
Cycling
With cycling, work phases of 30 s and recovery phases of 60 s may be useful with an intensity of the 50% of maximum short-term exercise capacity, determined with the patient starting with unloaded pedalling for 3 min and then increasing the work rate by 25 W every 10 s. During the recovery phase, patients pedal at 10 W
Treadmill
On a treadmill, work and recovery phases of 60 s each may be used

when not tolerated should be an angiotensin receptor antagonist.

Changes in systolic and diastolic blood pressure and increases in serum creatinine are usually small in normotensive patients. Moderate renal insufficiency and a relatively low blood pressure (serum creatinine up to 250 μmol/L and systolic blood pressure as low as 90 mmHg) are not contraindications to ACE-inhibitor treatment. Serum creatinine might increase by 10–15% in patients with severe heart failure, irrespective of baseline serum creatinine.[194] In most of these patients, creatinine levels either will remain stable or decrease towards pre-treatment values during continued treatment. It should be stressed that mortality is higher among patients with elevated creatinine levels and that these patients in particular benefit from treatment with ACE-inhibitors.[195] The risk of hypotension and renal dysfunction increases in patients with severe heart failure, those treated with high doses of diuretics, elderly patients and patients with renal dysfunction or hyponatraemia. Changes in serum potassium are usually small (0.2 mmol/L). Whereas mild hyperkalaemia is not a contraindication to use ACE-inhibitors, serum potassium levels >5.5 mmol/L are. If potassium-sparing diuretics were prescribed to correct serum potassium levels, they should be discontinued during initiation of ACE-inhibitor therapy.

ACE-inhibitor treatment is contraindicated in the presence of bilateral renal artery stenosis and angioedema during previous ACE-inhibitor therapy (Class of recommendation III, level of evidence A).

The effect of ACE-inhibition in heart failure has been documented in target doses that are usually higher than those used in clinical practice. Furthermore, in the ATLAS trial the first secondary endpoint was death or all-cause hospitalization which was reduced in patients with a higher than a lower dose regimen.[196] Target maintenance dose ranges of ACE-inhibitors shown to be effective in various trials are given in *Table 13*.

Recommended initiating and maintenance dosages of ACE-inhibitors which have documented effect of heart failure in Europe are presented in *Table 12*.

The dose of ACE-inhibitors should always be initiated at the lower dose level and titrated to the target dose. The recommended procedures for starting an ACE-inhibitor are given in *Table 14*.

Initiating ACE-inhibitor therapy

The dose of the chosen ACE-inhibitor should be titrated up to the maximum target dose used in clinical trials. When initiating therapy, careful attention should be given to the locally approved prescribing information.

Regular monitoring of renal function is recommended: (1) before, 1–2 weeks after each dose increment and at 3–6-months interval, (2) when the dose of an ACE-inhibitor is increased or other treatments, which may affect renal function, are added e.g. aldosterone antagonist or angiotensin receptor blocker, (3) in patients with past or present renal dysfunction or electrolyte disturbances more frequent measurements should be made, or (4) during any hospitalization.

Table 12 Doses of ACE-inhibitors shown to be effective in large, controlled trials of heart failure or left ventricular dysfunction

Studies of mortality	Drug	Target dose	Mean daily dose
Studies in CHF			
CONSENSUS Trial Study Group, 1987[192]	Enalapril	20 mg b.i.d.	18.4 mg
V-HeFT II, 1991[243]	Enalapril	10 mg b.i.d.	15.0 mg
The SOLVD Investigators, 1991[353]	Enalapril	10 mg b.i.d.	16.6 mg
ATLAS, 1999[196]	Lisinopril	High dose:	32.5–35 mg daily
		Low dose:	2.5–5 mg daily
Studies after MI LV dysfunction with or without HF			
SAVE, 1992[188]	Captopril	50 mg t.i.d.	127 mg
AIRE, 1993[193]	Ramipril	5 mg b.i.d.	(not available)
TRACE, 1995 [189]	Trandolapril	4 mg daily	(not available)

Care should be taken in patients with low systolic blood pressure or serum creatinine above 250 μmol/L. Patients with a systolic level below 100 mmHg should have therapy initiated under specialist medical care. Modest, orthostatic hypotension may occur. Low blood pressures (<90 mmHg) during ACE-inhibitor treatment are acceptable if the patient is asymptomatic.

Table 13 Recommended ACE-inhibitor maintenance dose ranges for some agents approved for heart failure in Europe*

Drug	Initiating dose	Maintenance dose
Documented effects on mortality/hospitalization		
Captopril	6.25 mg t.i.d.	25–50 mg t.i.d.
Enalapril	2.5 mg daily	10 mg b.i.d.
Lisinopril	2.5 mg daily	5–20 mg daily
Ramipril	1.25–2.5 mg daily	2.5–5 mg b.i.d.
Trandolapril	1 mg daily	4 mg daily

*Manufacturers' or regulatory recommendations.

Diuretics

Loop diuretics, thiazides, and metolazone

- Diuretics are essential for symptomatic treatment when fluid overload is present and manifest as pulmonary congestion or peripheral oedema. The use of diuretics results in rapid improvement of dyspnoea and increased exercise tolerance (Class of recommendation I, level of evidence A).[197,198]
- There are no controlled, randomized trials that have assessed the effect on symptoms or survival of these agents. Diuretics should always be administered in combination with ACE-inhibitors and beta-blockers if tolerated (Class of recommendation I, level of evidence C).

Detailed recommendations and major side effects are outlined in *Tables 15* and *16*.

Loop diuretics, thiazides, and metolazone are all used at various stages in the treatment of heart failure. Compared with control groups, patients treated with diuretics had a reduced risk of worsening heart failure and an improved exercise tolerance. There was also a trend for lower mortality in small trials.[199] Mild heart failure can be treated with a thiazide diuretic, but as heart failure worsens, a loop diuretic is usually necessary. At equivalent doses, all loop diuretics produce a comparable increase in urine output. Patients with severe heart failure often require increasing doses of loop diuretics. This may be caused by worsening renal function or decreased gastrointestinal absorption of furosemide. In such cases, replacement of furosemide by torasemide can be a solution because the bio-availability of the latter loop diuretic is not reduced in patients with heart failure.[200] Because of the better absorption of torasemide, a more stable diuretic treatment may be achieved with a reduction of re-admissions for heart failure.[201] Intravenous drug administration, and in particular continuous intravenous infusion of a loop diuretic, also often overcomes the diuretic resistance.[358]

Thiazide diuretics are less effective if the glomerular filtration rate falls below 30 mL/min, a situation that is commonly encountered in elderly patients with heart failure. In severe heart failure, thiazides have a synergistic effect with loop diuretics and may be used in combination.[202] It is probable that this combination is superior in terms of efficacy or adverse effect to increasing the dose of a loop diuretic. Metolazone is a powerful diuretic, which is often used as a drug of last resort added to loop diuretics; however, metolazone is not available in all European countries. Worsening renal function and hyponatraemia may occur as a consequence of overuse of loop diuretics or diuretic combinations.

Potassium-sparing diuretics

- Potassium-sparing diuretics should only be prescribed if hypokalaemia persists despite ACE-inhibition, or in severe heart failure despite the combination ACE-inhibition and low-dose spironolactone (Class of recommendation I, level of evidence C).
- Potassium supplements are generally ineffective in this situation (Class of recommendation III, level of evidence C).

Most patients on diuretics for heart failure will also be treated with an ACE-inhibitor. Until recently, the combination of potassium sparing diuretics and ACE-inhibitors

Table 14 The recommended procedure for starting an ACE-inhibitor or an angiotensin receptor blocker

Review the need for and dose of diuretics and vasodilators
Avoid excessive diuresis before treatment. Consider reducing or withholding diuretics, if being used, for 24 h
It may be advisable to start treatment in the evening, when supine, to minimize the potential negative effect on blood pressure, although there are no data in heart failure to support this. When initiated in the morning, supervision for several hours with blood pressure control is advisable in risk patients with renal dysfunction or low blood pressure
Start with a low dose (*Table 13*) and build up to maintenance dosages shown to be effective in large trials (*Table 12*)
If renal function deteriorates substantially, stop treatment
Avoid potassium-sparing diuretics during initiation of therapy
Avoid NSAIDs or coxibs
Check blood pressure, renal function, and electrolytes 1–2 weeks after each dose increment, at 3 months, and subsequently at 6 regular monthly intervals
The following patients should be referred for specialist care:
Cause of heart failure unknown
Systolic blood pressure $<$100 mmHg
Serum creatinine $>$150 μmol/L
Serum sodium $<$135 mmol/L
Severe heart failure
Valve disease as primary cause

Table 15 Diuretics

Initial diuretic treatment
Loop diuretics or thiazides. Always administered in addition to an ACE-inhibitor
If GFR $<$30 mL/min do not use thiazides, except as therapy prescribed synergistically with loop diuretics
Insufficient response:
increase dose of diuretic
combine loop diuretic and thiazide
with persistent fluid retention: administer loop diuretic twice daily
in severe heart failure add metolazone with frequent measurement of creatinine and electrolytes
Potassium-sparing diuretics: triamterene, amiloride, spironolactone
Use only if hypokalaemia persists after initiation of therapy with ACE-inhibitors and diuretics
Start 1-week low-dose administration; check serum potassium and creatinine after 5–7 days and titrate accordingly. Recheck every 5–7 days until potassium values are stable

GFR = glomerular filtration rate.

was regarded as potentially dangerous. One small, controlled study suggests that the administration of spironolactone at dosages that result in diuresis and natriuresis (i.e. 50–100 mg) may result in rapid weight reduction without hyperkalaemia in patients who are not responding to loop diuretics and ACE-inhibitors.[203] Accordingly, lower doses of spironolactone are not considered as potassium-sparing agents (described succeedingly). At present, potassium-sparing diuretics, such as triamterene, amiloride, and relatively high dosages of spironolactone, should only be considered if there is persisting diuretic-induced hypokalaemia despite concomitant ACE-inhibitor therapy, or in severe heart failure despite concomitant ACE-inhibition plus low-dose spironolactone. Similar restrictions also pertain in case of intolerance of ACE-inhibition and replacement therapy with angiotensin receptor blockers. Oral potassium supplements are less effective in maintaining body potassium stores during diuretic treatment.[204] In general, the use of all potassium-sparing diuretics should be monitored by repeated measurements of serum creatinine and potassium. A practical approach is to measure serum creatinine and potassium every 5–7 days after initiation of treatment until the values are stable. Thereafter, measurements can be made every 3–6 months.

Beta-adrenoceptor antagonists

- Beta-blocking agents are recommended for the treatment of all patients (in NYHA class II–IV) with stable, mild, moderate, and severe heart failure from ischaemic or non-ischaemic cardiomyopathies and reduced LVEF on standard treatment, including diuretics and ACE-inhibitors, unless there is a contraindication (Class of recommendation I, level of evidence A).
- Beta-blocking therapy reduces hospitalizations (all, cardiovascular and heart failure), improves the functional class and leads to less worsening of heart failure. This beneficial effect has been consistently observed in subgroups of different age, gender, functional class, LVEF, and ischaemic or non-ischaemic aetiology (Class of recommendation I, level of evidence A).
- In patients with left ventricular systolic dysfunction, with or without symptomatic heart failure, following an acute myocardial infarction long-term beta-blockade is recommended in addition to ACE-inhibition to reduce mortality (Class of recommendation I, level of evidence B).[205]
- Differences in clinical effects may be present between different beta-blockers in patients with heart failure.[206,207] Accordingly, only bisoprolol, carvedilol, metoprolol succinate, and nebivolol can be recommended (Class of recommendation I, level of evidence A).

Extensive information is now available of the additional value of beta-blockers on top of background ACE-inhibitor therapy if tolerated. In several large randomized placebo-controlled mortality trials, carvedilol,[208–210] bisoprolol,[211] and metoprolol succinate[212,213] have been associated with a long-term reduction in total mortality, cardiovascular mortality, sudden death and death that is caused by progression of heart failure in patients in functional class II–IV. In these studies, beta-blocking therapy also reduces hospitalizations (all, cardiovascular and heart failure), improves the functional class and leads to less worsening of heart failure than placebo. This beneficial effect has been consistently observed in subgroups

Table 16 Diuretics (oral): dosages and side-effects

	Initial dose (mg)		Maximum recommended daily dose (mg)		Major side effects
Loop diuretics					
Furosemide	20–40		250–500		Hypokalaemia, hypomagnesaemia, hyponatraemia
Bumetanide	0.5–1.0		5–10		Hyperuricaemia, glucose intolerance
Torasemide	5–10		100–200		Acid–base disturbance
Thiazides					
Bendroflumethiazide	2.5		10		
Hydrochlorothiazide	25		50–75		Hypokalaemia, hypomagnesaemia, hyponatraemia
Metolazone	2.5		10		Hyperuricaemia, glucose intolerance
Indapamide	2.5		5		Acid–base disturbance
Potassium-sparing diuretic	+ACEI	−ACEI	+ACEI	−ACEI	
Amiloride	2.5	5	20	40	Hyperkalaemia, rash
Triamterene	25	50	100	200	Hyperkalaemia
Spironolactone	12.5–25	50	50	100–200	Hyperkalaemia, gynaecomastia, zbreast pain

of different age, gender, functional class, LVEF, and ischaemic or non-ischaemic aetiology (Class of recommendation I, level of evidence A).[214] Beta-blockers are the only heart failure drugs that cause a significant improvement of LVEF, which occurs both in patients with ischaemic and non-ischaemic aetiology of heart failure.[215]

However, the improved left ventricular systolic function does not constantly result in a better exercise capacity probably because of the negative chronotropic effects of beta-blockers.

A reduction in mortality and hospitalization has been demonstrated with several beta-blockers in CHF, although the size of the treatment effect can differ between agents. In SENIORS, nebivolol significantly reduced the composite outcome of death or cardiovascular hospitalizations in elderly patients across reduced and preserved ejection fractions.[216] In one large trial, no significant benefit on survival was observed with bucindolol.[206] A direct comparison between carvedilol and metoprolol tartrate has been reported in Carvedilol Or Metoprolol European Trial (COMET).[207] In this double-blind, randomized parallel group trial over 58 months all-cause mortality was 34% for carvedilol and 40% for metoprolol (hazard ratio 0.83 [95% CI 0.74–0.93] $P = 0.0017$). In contrast, the composite endpoint of mortality and all-cause admission was not different in the two treatment groups (74% on carvedilol and 76% on metoprolol, $P = 0.122$).

COMET provides further support for using documented beta-blockers as titrated in trials. Accordingly, metoprolol tartrate is not recommended for use in treatment of CHF at doses used in COMET. Accordingly, only bisoprolol, carvedilol, and metoprolol succinate can be recommended at present (Class of recommendation I, level of evidence A, class I).

A further argument for a more consequent use of beta-blockers is the observation that they have an additive effect to ACE-inhibitors and the combination reduces cardiovascular mortality and hospitalizations for heart failure more than ACE-inhibitors alone. This was clearly documented by secondary analyses of the SOLVD[217] and SAVE trials.[218]

Initiation of therapy

As beta-blocker action may be biphasic with long-term improvement, possibly preceded by initial worsening, beta-blockers should be initiated under careful control. The initial dose should be small and increased slowly and progressively to the target dose used in the large clinical trials. Up-titration should be adapted to individual responses. Analysis of the dose response effects in the MERIT[219] and CIBIS II trials[220]also showed mortality reductions in the lower dose groups. Therefore, it is evident that even a low dose of a beta-blocker is superior to a treatment without beta-blocker administration. The introduction of beta-blockers should, therefore, always be attempted even if the titration period has to be prolonged.

Beta-blockers may reduce heart rate excessively, may temporarily induce myocardial depression and precipitate heart failure. In addition, beta-blockers may initiate or exacerbate asthma and induce peripheral vasoconstriction. *Table 17* gives the recommended procedure for the use of beta-blockers in clinical practice and contraindications. *Table 18* shows the titration scheme of the drugs used in the most relevant studies.

Aldosterone receptor antagonists

- Aldosterone antagonists are recommended in addition to ACE-inhibitors, beta-blockers, and diuretics in advanced heart failure (NYHA III–IV) to improve survival and morbidity (Class of recommendation I, level of evidence B).
- Aldosterone antagonists are recommended in addition to ACE-inhibition and beta-blockade in heart failure after myocardial infarction with left ventricular systolic dysfunction and signs of heart failure or diabetes

to reduce mortality and morbidity (Class of recommendation I, level of evidence B).

Although spironolactone was developed as a diuretic agent at a higher dose level, it is now understood that aldosterone has an important role in the pathophysiology of heart failure. It promotes vascular and myocardial fibrosis, potassium and magnesium depletion, sympathetic activation, parasympathetic inhibition, and baroreceptor dysfunction. ACE-inhibitors insufficiently suppress circulating aldosterone levels.

The RALES mortality trial showed that low-dose spironolactone (12.5–50 mg) on top of an ACE-inhibitor, a loop diuretic and digoxin markedly and progressively improved survival of patients in advanced (NYHA class III–IV) heart failure, irrespective of aetiology.[221] At this dose, spironolactone is believed not to have an appreciable diuretic effect. Both death from progressive heart failure and sudden cardiac death were reduced in RALES, and although only 11% received a beta-blocker, the mortality reduction was significant in this prespecified subgroup. Whether an aldosterone antagonist is of proven benefit in patients with class II heart failure or asymptomatic left ventricular dysfunction remains to be established. In the EPHESUS trial, 6 632 patients with reduced ejection fraction and heart failure (or diabetes) post-infarction were enrolled.[222] This trial utilized eplerenone, which blocks more selectively the mineralcorticoid receptor, rather than glucocorticoid, progesterone or androgen receptors. In EPHESUS, the effect of eplerenone in a dose of 25–50 mg daily demonstrated a 15% significant reduction in mortality as well as the number of patients hospitalized for heart failure. The findings were also evident on sudden death, in particular among patients with an ejection fraction $<30\%$. The safety profile of eplerenone is better in this context for eplerenone with no increased risk of gynaecomastia.

Administration and dosing considerations for aldosterone antagonists are provided in *Table 19*.

Adverse effects of spironolactone

If painful gynaecomastia develops (10% in RALES), spironolactone may need to be stopped. Both spironolactone and eplerenone increase the risk of severe hyperkalaemia but reduce the risk of hypokalaemia, which emphasizes the need for monitoring.[223] Therefore, the outcome trials with spironolactone and eplerenone excluded patients with serum creatinine >221 μmol/L (2.5 mg/dL) and serum potassium >5 mmol/L. When spironolactone was more widely used, an increased risk of hyperkalaemia has been reported.[224]

Angiotensin II receptor blockers

For patients with left ventricular systolic dysfunction:

- Angiotensin II receptor blockers (ARBs) can be used as an alternative to ACE-inhibition in symptomatic patients intolerant to ACE-inhibitors to improve morbidity and mortality (Class of recommendation I, level of evidence B).
- ARBs and ACE-inhibitors seem to have similar efficacy in CHF on mortality and morbidity (Class of recommendation IIa, level of evidence B).
- In acute myocardial infarction with signs of heart failure or left ventricular dysfunction ARBs and ACE-inhibitors have similar or equivalent effects on mortality (Class of recommendation I, level of evidence A).
- ARBs can be considered in combination with ACE-inhibitors in patients who remain symptomatic to reduce mortality (Class of recommendation IIa, level of evidence B)

Table 17 The recommended procedure for starting a beta-blocker

I	Patients should be on a background therapy with ACE inhibition, if not contraindicated
II	The patient should be in a relatively stable condition, without the need of intravenous inotropic therapy and without signs of marked fluid retention
III	Start with a very low dose (*Table 18*) and titrate up to maintenance dosages shown to be effective in large trials. The dose may be doubled every 1–2 weeks if the preceding dose was well tolerated. Most patients can be managed as out-patients
IV	Transient worsening failure, hypotension, or bradycardia may occur during the titration period or thereafter
	a Monitor the patient for evidence of heart failure symptoms, fluid retention, hypotension, and symptomatic bradycardia
	b If worsening of symptoms, first increase the dose of diuretics or ACE-inhibitor; temporarily reduce the dose of beta-blockers if necessary
	c If hypotension, first reduce the dose of vasodilators; reduce the dose of the beta-blocker if necessary
	d Reduce or discontinue drugs that may lower heart rate in presence of bradycardia; reduce dose of beta-blockers if necessary, but discontinue only if clearly necessary
	e Always consider the reintroduction and/or uptitration of the beta-blocker when the patient becomes stable
V	If inotropic support is needed to treat a decompensated patient on beta-blockade, phosphodiesterase inhibitors should be preferred because their haemodynamic effects are not antagonized by beta-blocker agents
The following patients should be referred for specialist care	
	a Severe heart failure Class III/IV
	b Unknown aetiology
	c Relative contraindications: asymptomatic bradycardia and/or low blood pressure
	d Intolerance to low doses
	e Previous use of beta-blocker and discontinuation because of symptoms
	f Suspicion of bronchial asthma or severe pulmonary disease
Contraindications to beta-blockers in patients with heart failure	
	g Bronchial asthma
	h Severe bronchial disease
	i Symptomatic bradycardia or hypotension

Table 18 Initiating dose, target dose, and titration scheme of beta-blocking agents as used in recent large, controlled trials

Beta-blocker	First dose (mg)	Increments (mg/day)	Target dose (mg/day)	Titration period
Bisoprolol [211]	1.25	2.5, 3.75, 5, 7.5, 10	10	Weeks–month
Metoprolol succinate CR[212]	12.5/25	25, 50, 100, 200	200	Weeks–month
Carvedilol[210]	3.125	6.25, 12.5, 25, 50	50	Weeks–month
Nebivolol[216]	1.25	2.5, 5, 10	10	Weeks–month

Daily frequency of administration as in the trials referenced here.

and hospital admissions for heart failure (Class of recommendation I, level of evidence A).

In NYHA class III patients remaining symptomatic despite therapy with diuretics, ACE-inhibitors, and beta-blockers, there is no definite evidence as to whether the addition of an ARB or aldosterone antagonist will further reduce hospitalization for heart failure or mortality. Concerns raised by initial studies about a potential negative interaction between ARBs and beta-blockers have not been confirmed by recent studies in post-myocardial infarction or CHF.

ARBs vs. placebo

In symptomatic patients with CHF intolerant to ACE-inhibitors because of cough, symptomatic hypotension, or renal dysfunction candesartan significantly reduced cardiovascular death or hospital admission for heart failure, whereas the rate of discontinuation of the study drug was similar to placebo.[225] In all patients with symptomatic heart failure, irrespective of background ACE-inhibitor or beta-blocker therapy, candesartan reduced all-cause mortality, particularly among those with left ventricular systolic dysfunction.[226] Further, hospital admissions for heart failure were reduced significantly.[227] In another trial valsartan improved significantly the combined endpoint of mortality and morbidity and mortality alone in the small subgroup of patients not receiving an ACE-inhibitor.[228,229]

ARBs vs. ACE-inhibitors

The direct comparison of the two classes was assessed in Elite II in CHF and showed that Losartan was not as effective as Captopril, although the rate of discontinuation for adverse effects was reduced.[230] Together with smaller trials, meta-analyses show similar efficacy on mortality and morbidity.[231,232] Two trials evaluated ARBs against ACE-inhibition in post-myocardial infarction with left ventricular dysfunction or signs of heart failure. The direct comparison of losartan with captopril indicated that losartan was not as effective as captopril on all-cause mortality,[233] whereas valsartan, although not superior, was demonstrated to be as effective as captopril on the same outcome in the second trial.[234]

ARBs on top of ACE-inhibitors

Addition of ARBs on top of ACE-inhibitors in patients remaining symptomatic improves morbidity and mortality. In Val-HeFT addition of valsartan to background therapy, including ACE-inhibitors, reduced significantly heart failure hospitalizations and improved signs/symptoms of heart failure and quality of life.[229] In CHARM added, candesartan on top of ACE-inhibitors significantly reduced the primary outcome of cardiovascular death or hospital admission for heart failure by 15% and each component of the primary composite in patients with reduced ejection fraction.[235] These results, together with meta-analysis,[231,232] suggest the beneficial role of the dual inhibition of the renin angiotensin system through ACE-inhibition and Angiotensin II receptor blockade in patients remaining symptomatic under ACE-inhibitors alone. The higher rate of discontinuation because of dizziness/hypotension, renal impairment or hyperkalaemia in both trials in the combination arm indicates the need for careful monitoring of blood pressure, renal function and potassium levels in these patients. In post-myocardial infarction with left ventricular dysfunction or heart failure (VALIANT), the combination of an ARB with an ACE-inhibitor had similar efficacy compared with treatment with each agent alone but was associated with a higher incidence of side-effects.

Table 19 Administration and dosing considerations with aldosterone antagonists (spironolactone, eplerenone)

- Consider whether a patient is in severe heart failure (NYHA III–IV) despite ACE-inhibition/diuretics
- Check serum potassium ($<$5.0 mmol/L) and creatinine ($<$250 μmol/L)
- Add a low dose (spironolactone 12.5–25 mg, eplerenone 25 mg) daily
- Check serum potassium and creatinine after 4–6 days
- If at any time serum potassium 5–5.5 mmol/L, reduce dose by 50%. Stop if serum potassium $>$5.5 mmol/L
- If after 1 month symptoms persist and normokalaemia exists, increase to 50 mg daily. Check serum potassium/creatinine after 1 week

ARBs and beta-blockers

Early studies, including ELITE II and Val-HeFT, suggested a trend towards a negative effect of the combinations losartan with beta-blocker or valsartan with ACE-inhibitor and beta-blocker. However, such an interaction was not observed in the OPTIMAAL trial in post-

myocardial infarction for the combination losartan with beta-blocker, in CHARM added for the combination candesartan with ACE-inhibitor and beta-blocker in CHF, and in VALIANT for the combination valsartan with captopril and beta-blocker.

Therefore, there is no evidence that the combinations ARBs and beta-blockers or ARBs, ACE-inhibitors, and beta-blockers have a deleterious effect in either CHF or post-myocardial infarction.

Dosing

The fact that the doses of losartan used in ELITE II and OPTIMAAL (target dose 50 mg) were not as effective as the ACE-inhibitor captopril, whereas high doses of candesartan (target dose 32 mg once daily) or valsartan (up to 160 mg twice daily) were associated with a significant improvement in cardiovascular morbidity-mortality (CHARM added and alternative) or heart failure morbidity (Val-HeFT) on top of ACE-inhibition raises the hypothesis that high target doses of ARBs are required to result in a beneficial effect in CHF or to be as effective as ACE-inhibition in this setting (*Table 20*).

Initiation and monitoring of ARBs, which are outlined in *Table 14*, are similar to procedures for ACE-inhibitors.

Table 20 Currently available angiotensin II receptor antagonists

Drug	Daily dose (mg)
Documented effects on mortality/morbidity	
Candesartan[227]	4–32
Valsartan[229]	80–320
Also available	
Eprosartan[354]	400–800
Losartan[177,230]	50–100
Irbesartan[355]	150–300
Telmisartan[356]	40–80

Cardiac glycosides

- Cardiac glycosides are indicated in atrial fibrillation and any degree of symptomatic heart failure, whether or not left ventricular dysfunction is the cause. Cardiac glycosides slow the ventricular rate, which improves ventricular function and symptoms (Class of recommendation I, level of evidence B).[236]
- A combination of digoxin and beta-blockade appears superior to either agent alone in patients with atrial fibrillation (Class of recommendation IIa, level of evidence B).[237]
- Digoxin has no effect on mortality but may reduce hospitalizations and, particularly, worsening heart failure hospitalizations, in the patients with heart failure caused by left ventricular systolic dysfunction and sinus rhythm treated with ACE-inhibitors, beta-blockers, diuretics and, in severe heart failure, spironolactone (Class of recommendation IIa, level of evidence A).

Digoxin and digitoxin are the most frequently used cardiac glycosides. They have identical pharmacodynamic effects but different pharmacokinetic profiles. Elimination of digoxin is renal. In contrast, digitoxin is metabolized in the liver and is less dependent of renal function, potentially useful in renal dysfunction and in elderly patients. Clinical trials referred here have been carried out with digoxin.

In the DIG trial in 6 800 patients with an ischaemic and non-ischaemic cardiomyopathy and mild to moderate heart failure, long-term digoxin did not improve survival. Furthermore, a small decrease in the risk of death from heart failure was offset by an increase in the risk of death from other causes. A significant reduction, however, was observed for hospitalizations for worsening heart failure as well as all-cause hospitalizations and total number of hospitalizations per patient.[238] A later report from this trial suggests an increased risk of death in women but not in men by digoxin.[239] Another report suggested that better effect was observed with serum digoxin <0.5 ng/mL compared with >0.9 ng/mL.[240] Thus, the primary benefit and indication of digoxin in heart failure is the reduction of symptoms and improvement of the clinical status, and thereby to decrease the risk of hospitalization for heart failure without an impact on survival.[241]

Contraindications to the use of cardiac glycosides include bradycardia, second- and third-degree AV block, sick sinus syndrome, carotid sinus syndrome, Wolff–Parkinson–White syndrome, hypertrophic obstructive cardiomyopathy, hypokalaemia, and hyperkalaemia, as this may increase malignant arrhythmias.

Digoxin

The usual daily dose of oral digoxin is 0.125–0.25 mg if serum creatinine is in the normal range (in the elderly 0.0625–0.125 mg, occasionally 0.25 mg). No loading dose is needed when treating chronic conditions. The treatment can also be initiated with 0.25 mg bid for 2 days. Renal function and plasma potassium should always be measured before starting treatment. In renal failure, the daily doses should be reduced accordingly. As the digoxin clearance closely approximates to the creatinine clearance, the latter should be measured or calculated as provided in *Table 3*.

Vasodilator agents in CHF

- There is no specific role for direct-acting vasodilators in the treatment of CHF (Class of recommendation III, level of evidence A).

Hydralazine-isosorbide dinitrate

- Vasodilator agents may be used as adjunctive therapy in the management of heart failure. In case of intolerance of ACE-inhibitors and ARBs, the combination hydralazine/nitrates can be tried (Class of recommendation I, level of evidence B).

Relatively high doses of hydralazine (up to 300 mg) in combination with high-dose isosorbide dinitrate (up to 160 mg) without ACE-inhibition may have some beneficial

effects on mortality, but not on hospitalization for heart failure.[242] At these doses, the combination increased exercise performance more when compared with enalapril.[243] In African-American patients the administration of 1–2 tablets tid of the fixed doses combination of isosorbide dinitrate (20 mg) and hydralazine (37.5 mg) reduced mortality and morbidity and improved quality of life.[244]

Nitrates

- Nitrates may be used as adjunctive therapy for angina or relief of dyspnea (Class of recommendation IIa, level of evidence C). Evidence that oral nitrates improve symptoms of heart failure chronically or during an acute exacerbation is lacking.

Early development of haemodynamic tolerance (tachyphylaxis) to nitrates may occur with frequent dosing (every 4–6 h), but is less with intervals of 8–12 h[245] or in conjunction with ACE-inhibitors or hydralazine.[246]

Alpha-adrenergic blocking drugs

- There is no evidence to support the use of alpha-adrenergic blocking drugs in heart failure (Class of recommendation III, level of evidence B).[242]

Calcium antagonists

- In heart failure caused by systolic dysfunction, calcium antagonists are not recommended for the treatment of heart failure. Diltiazem- and verapamil-type calcium antagonists in particular are not recommended in heart failure because of systolic dysfunction; they are contraindicated in addition to beta-blockade (Class of recommendation III, level of evidence C).
- Newer calcium antagonists (felodipine and amlodipine) in addition to baseline therapy, including ACE-inhibitors and diuretics, do not provide a better effect on survival when compared with placebo (Class of recommendation III, level of evidence A).[247,248]

As long-term safety data with felodipine and amlodipine indicate a neutral effect on survival, they may be considered as additional therapy for concomitant arterial hypertension or angina not controlled by nitrates and beta-blockers.

Nesiritide

Recently, nesiritide, a new class of vasodilator, has been developed for the treatment of decompensated heart failure. Nesiritide is a recombinant human brain or B-type natriuretic peptide that is identical to the endogenous hormone produced by the ventricle. Nesiritide has venous, arterial, and coronary vasodilatory properties that reduce preload and afterload, and increase cardiac output without direct inotropic effects.

The drug has been shown to be efficacious in improving subjective dyspnoea score as well as inducing significant vasodilation when administered intravenous to patients with acute heart failure (AHF). Clinical experience with nesiritide is still limited. Nesiritide may cause hypotension and some patients are non-responders. Effects of nesiritide has not been demonstrated on clinical outcome.[249]

Positive inotropic therapy

- Repeated or prolonged treatment with oral inotropic agents increases mortality and is not recommended in CHF (Class of recommendation III, level of evidence A).
- Intravenous administration of inotropic agents is commonly used in patients with severe heart failure with signs of both pulmonary congestion and peripheral hypoperfusion. However, treatment-related complications may occur and their effect on prognosis is uncertain; depending on agent level of evidence and strength of recommendation varies.[21]

Intravenous inotropic therapy is used to correct the haemodynamic disturbances of severe episodes of worsening heart failure. The agent most often used in this setting is dobutamine. However, its use has been insufficiently documented in controlled trials and the effects of dobutamine on prognosis are not well characterized (Class of recommendation IIb, level of evidence C). Problems related to use of dobutamine are tachyphylaxis, increase in heart rate, induction of malignant tachyarrhythmias, and/or myocardial ischaemia. Its mechanisms of action through beta-adrenergic receptor stimulation also makes it less effective in the patients on concomitant beta-blocker treatment.

Phosphodiesterase inhibitors like milrinone or enoximone may be more effective in the patients on concomitant beta-blocker treatment and have a peripheral and coronary vasodilating activity which may have favorable effects (i.e. greater decline in pulmonary pressures, lower incidence of myocardial ischaemia). However, they also are associated with atrial and ventricular tachyarrhythmias and an increase in myocardial oxygen consumption. Excessive peripheral vasodilation may cause hypotension.[250]

In AHF intravenous milrinone does not reduce the number of hospitalizations or cardiovascular events, but leads to a higher incidence of treatment-related complications (e.g. atrial fibrillation and hypotension) when compared with placebo.[251]

The newer calcium sensitizer levosimendan is indicated in patients with symptomatic low cardiac output secondary to cardiac systolic dysfunction without severe hypotension compared with phosphodiesterase inhbitors, levosimendan has peculiar calcium sensitizing and peripheral vasodilator activities. It has been shown to have greater haemodynamic efficacy and to better affect outcome in a double-blind comparison trial with dobutamine.[252]

In studies with oral treatment, milrinone, enoximone, vesnarinone and amrinone invariably increase arrhythmias and mortality.

Anti-thrombotic agents

- In CHF associated with atrial fibrillation, a previous thromboembolic event or a mobile left ventricular thrombus, anti-coagulation is firmly indicated (Class of recommendation I, level of evidence A).[253]
- There is little evidence to show that anti-thrombotic therapy modifies the risk of death or vascular events in patients with heart failure.
- In patients with CHF who have underlying coronary artery disease, anti-platelet agents for prevention of myocardial infarction and death are recommended (Class of recommendation IIa, level of evidence B).[254]
- Oral anti-coagulants should be preferred in patients with previous myocardial infarction and a left ventricular mural thrombus (Class of recommendation IIa, level of evidence C).
- After a prior myocardial infarction, either aspirin or oral anti-coagulants are recommended as secondary prophylaxis (Class of recommendation IIa, level of evidence C).
- Aspirin should be avoided in patients with recurrent hospitalization with worsening heart failure (Class of recommendation IIb, level of evidence B).

Patients with CHF are at high risk of thromboembolic events. Factors predisposing to thromboembolism are low cardiac output with relative stasis of blood in dilated cardiac chambers, poor contractility, regional wall motion abnormalities, and atrial fibrillation, if present.[255]

Ischaemic heart disease is the commonest cause of heart failure and coronary vascular occlusion is the commonest vascular event in this population. The annual risk of myocardial infarction in CHF is estimated from 2 to 5.4%. The reported annual risk of stroke in controlled heart failure studies is between 1 and 2% vs. an annual risk of stroke $<0.5\%$ in the general population aged 50–75 years. Both in the Vasodilators in Heart Failure trials (V-HeFT)[242,243] and in the SAVE[188] study the risk of stroke was increased in older patients or in those who had a lower ejection fraction.[256] The annual risk of stroke in the Stroke Prevention of Atrial Fibrillation study (SPAF) was 10.3% in atrial fibrillation patients with definite heart failure and 17.7% in those with recent heart failure.[257] Left ventricular thrombi are detected by transthoracic echocardiography in CHF patients with a prevalence that varies markedly in different studies from $>40\%$ to $<3\%$; whether evidence of ventricular thrombus confers an increased risk of embolization in this setting remains controversial, with several studies suggesting a low risk of additional events.[256,258,259] More precisely, there is little evidence to suggest that patients with a layered left ventricular thrombus are at increased risk of thromboembolic events, whereas the risk is increased in patients with mobile intracardiac thrombi.

There is little evidence to support the concomitant treatment with an ACE-inhibitor and aspirin in heart failure.[260–262]

However, the rates of thromboembolic complications in heart failure are sufficiently low to limit the evaluation of any potential beneficial effect of anti-coagulation/anti-thrombotic therapy in these patients.

Anti-arrhythmics

Anti-arrhythmic drugs other than beta-blockers are generally not indicated in patients with CHF. In patients with atrial fibrillation (rarely flutter) or non-sustained or sustained ventricular tachycardia treatment with anti-arrhythmic agents may be indicated.

Class I anti-arrhythmics

- Class I anti-arrhythmics should be avoided as they may provoke fatal ventricular arrhythmias, have an adverse haemodynamic effect and reduce survival in heart failure (Class of recommendation III, level of evidence B).[263]

Class II anti-arrhythmics

- Beta-blockers reduce sudden death in heart failure (Class of recommendation I, level of evidence A)[264] (see also page 23).
- Beta-blockers may also be indicated alone or in combination with amiodarone or non-pharmacological therapy in the management of sustained or non-sustained ventricular tachy-arrhythmias (Class of recommendation IIa, level of evidence C).[265]

Class III anti-arrhythmics

- Amiodarone is effective against most supraventricular and ventricular arrhythmias (Class of recommendation I, level of evidence A). It may restore and maintain sinus rhythm in patients with heart failure and atrial fibrillation even in the presence of enlarged left atria, or improve the success of electrical cardioversion. Amiodarone is the preferred treatment in this condition.[266,267] Amiodarone is the only anti-arrhythmic drug without clinically relevant negative inotropic effects.
- Routine administration of amiodarone in patients with heart failure is not justified (Class of recommendation III, level of evidence A).

Large trials have shown that prophylactic use of amiodarone in patients with non-sustained, asymptomatic ventricular arrhythmias and heart failure does not affect total mortality.[268,269] The risk of organ toxicity, such as hyper- and hypothyroidism, hepatitis, pulmonary fibrosis, and neuropathy, although shown to be relatively low in recent, large, placebo-controlled trials, must be weighed against the potential benefits of amiodarone. Lower doses (100–200 mg/day) may reduce the risk.

Dofetilide, a new class III agent, was found to be safe in heart failure patients as no modification of total mortality was noted. However, the incidence of torsades de pointe was increased.[270]

Oxygen therapy

- Oxygen is used for the treatment of AHF, but in general has no application in CHF (Class of recommendation III, level of evidence C).

Oxygen supplementation may lead to haemodynamic deterioration in patients with heart failure who are free of pulmonary oedema.[271] In patients with cor pulmonale, long-term oxygen therapy has been shown to reduce mortality.[272]

Surgery and devices

Revascularization procedures, mitral valve surgery, and ventricular restoration

- If clinical symptoms of heart failure are present, surgically correctable pathologies must always be considered (Class of recommendation I, level of evidence C, class I).

Revascularization

- There are no data from multicentre trials to support the use of revascularization procedures for the relief of heart failure symptoms. Single centre, observational studies on heart failure of ischaemic origin, suggest that revascularization might lead to symptomatic improvement (Class of recommendation IIb, level of evidence C).
- Until the results of randomized trials are reported, revascularization (surgical or percutaneous) is not recommended as routine management of patients with heart failure and coronary disease. (Class of recommendation III, level of evidence C).

The pathophysiological rationale for revascularization includes improvement of the blood supply to myocardium affected by hibernation or ischaemia and, possibly, the reduction of the risk or size of recurrent myocardial infarction.[132,273] Accurate selection of patients whose left ventricular function is likely to improve after revascularization requires considerable skill and access to advanced cardiac imaging techniques including stress echocardiography, nuclear myocardial perfusion imaging or cardiac magnetic resonance imaging. Patients with left ventricular systolic dysfunction and heart failure are at considerable increased operative mortality.[273] There remains a strong negative correlation of operative mortality and LVEF as outlined in the analysis of the Society of Thoracic Surgeons database (WWW.CTSNET. ORG/). Here, a low LVEF ($<25\%$) was associated with an increased operative mortality. Also, advanced heart failure symptoms (NYHA IV) resulted in a greater mortality rate than in patients with mild to moderate heart failure.

A study comparing the effect of symptomatic heart failure with left ventricular dysfunction independently showed a stronger correlation of NYHA class with operative mortality than LVEF.[274]

Off pump coronary revascularization may lower the surgical risk of both cardiac and cerebral complications for patients with heart failure undergoing surgical revascularization, although randomized clinical trials have questioned the results of observational data.[274]

Clinicians may be able to justify revascularization of selected patients with heart failure on an individual patient basis for instance when left main coronary disease is present.

Mitral valve surgery

- Mitral valve surgery in patients with severe left ventricular systolic dysfunction and severe mitral valve insufficiency due to ventricular dilatation may lead to symptomatic improvement in selected heart failure patients (Class of recommendation IIb, level of evidence C).

Observational studies have indicated excellent early and up to 5 year outcome of mitral reconstruction in patients with end-stage cardiomyopathy.[275,276]

Left ventricular restoration

Anatomically, LV enlargement represents a key feature in patients with heart failure. Irrespective of the aetiology—dilative vs. ischaemic–the pathophysiology of LV enlargement results in increased wall tension, higher oxygen demand, and a tendency to ongoing dilatation. Surgical reduction of the size of the left ventricle has therefore been attempted by a variety of approached aiming at decreasing LV diameters and improving ejection fraction. Among these surgical techniques, myocardial resection can be distinguished from mitral valve repair techniques and external compression.

LV aneurysmectomy

- LV aneurysmectomy is indicated in patients with large, discrete left ventricular aneurysms who develop heart failure (Class of recommendation I, level of evidence C).

In the past, many patients with ischaemic cardiomyopathy have profited from LV aneurysmectomy, and the technique of Vincent Dor with resection of akinetic zones and not only diskynetic area (aneurysm), has been applied worldwide with improvement, also regarding of LV function and heart failure symptoms.[277, 278] Cooley's endoaneurysmorraphy has been shown in uncontrolled clinical series to improve symptoms and ventricular function in patients with dilated ischaemic heart disease. A registry of 662 left ventricular restoration procedures performed in 13 centres worldwide has recently showed favourable results in terms of hospital and mid-term mortality.[279]

More recently, a scientifically more sophisticated approach of "ventricular restoration" has been introduced into clinical practice by Buckberg.[280–283]

Cardiomyoplasty

- Cardiomyoplasty cannot be recommended for the treatment of heart failure or as a viable alternative to heart transplantation (Class of recommendation III, level of evidence C).

Cardiomyoplasty has only been applied in a very limited number of patients and is still undergoing investigation.

Class IV patients should be avoided because they have a high operative mortality.

Partial left ventriculectomy (Batista operation)

- Currently, partial ventriculectomy cannot be recommended for the treatment of heart failure or as an alternative to heart transplantion (Class of recommendation III, level of evidence C).

Partial, lateral resection of the left ventricle plus or minus mitral valve surgery initially gained interest for treatment of end-stage heart failure patients. However, in recent studies a number of patients required ventricular assist devices or subsequent transplantation for failed surgery.[284,285]

External ventricular restoration

- Currently, external ventricular restoration cannot be recommended for the treatment of heart failure. Preliminary data suggest an improvement in LV dimensions and NYHA class with some devices (Class of recommendation III, level of evidence C).

Two devices aiming at restricting enlargement of the failing heart and reducing wall stress have entered the clinical arena. Based on several successful animal experiments as well as a clinical study,[286] the myosplint technique was used in an early clinical study. Bisection of the left ventricle and creation of a smaller LV chamber resulted in significantly reduced LV wall stress.[287] Prospective outcome trials have to be awaited.

The Acorn external cardiac support device may reduce wall stress and preventing further LV remodelling in heart failure patients by an external polyester net.[288] Clinical data are still scarce but early experience would suggest significant improvement in LV dimensions and NYHA class.

Pacemakers

- Conventional right ventricular pacing has no established role in the treatment of heart failure except for conventional bradycardia indication (Class of recommendation III, level of evidence A).
- Resynchronization therapy using bi-ventricular pacing can be considered in patients with reduced ejection fraction and ventricular dyssynchrony (QRS width $\geq$120 ms), who remain symptomatic (NYHA III–IV) despite optimal medical therapy to improve symptoms (Class of recommendation I, level of evidence A), hospitalizations (Class of recommendation I, level of evidence A) and mortality (Class of recommendation I, level of evidence B).

Bi-ventricular pacing improves symptoms, exercise capacity, and reduces hospitalizations.[289,290] A beneficial effect on the composite of long-term mortality or all-cause hospitalization has recently been demonstrated,[291] as well as a significant effect on mortality.[357]

Conventional indication

Pacemakers have been used in patients with heart failure to treat bradycardia when conventional indications exist. Pacing only of the right ventricle in patients with systolic dysfunction will induce ventricular dyssynchrony and may increase symptoms. In retrospective studies, lower morbidity and prolonged survival by atrioventricular (AV) synchronous pacing have been reported in patients with chronic high degree AV block or sinus node disease and concomitant heart failure. However, prospective randomized controlled trials have not shown a reduction in the development of heart failure with AV synchronous pacing compared with only ventricular pacing.[292,293]

Resynchronization therapy

Approximately 20% of patients with severe heart failure will have a broad QRS complex ($\geq$120 ms) suggesting intra- or interventricular conduction disturbances. A large proportion of such patients will exhibit inter- or intraventricular dyssynchrony in ventricular contraction. Some patients with narrow QRS width will also have dyssynchrony. Many of these patients will have important mitral regurgitation.

Bi-ventricular pacing stimulates both ventricles near-simultaneously, improving the co-ordination of ventricular contraction, and reducing the severity of mitral regurgitation. Successful implantation of the device requires considerable skill and the procedure carries some hazard to the patient. Procedure-related mortality should be $<$1%.

Two substantial, double-blind trials have shown that bi-ventricular pacing improves symptoms and exercise capacity for at least 6 months in patients with reduced ejection fraction and a QRS width $\geq$120 ms and who remain symptomatic (NYHA III–IV) despite optimal medical therapy.[289,290,294]

In COMPANION, 1 520 patients in NYHA class III–IV, with LVEF$\leq$35% and with dyssynchrony as QRS duration $>$120 ms were randomized to continued optimal therapy [bi-ventricular pacing (CRT) or bi-ventricular pacing with an implantable cardioverter defibrillator (ICD) (CRT-D)]. The composite outcome of mortality or hospitalization for any reason was reduced by 20% in both pacing arms.[291] Mortality (secondary objective) was reduced by 24% relative (4% absolute) ($P = 0.06$) by CRT and 36% (7% absolute) ($P = 0.003$) by CRT-D during 16 month of follow-up. There was no difference in mortality when CRT and CRT-D were compared. Some patients derive no benefit from RCT even though they fit current selection criteria. The CARE-HF trial randomized 813 patients with ventricular dyssynchrony and/or QRS $\geq$ 150 ms demonstrating a significant 37% relative (16% absolute) reduction in the composite of death or hospitalizations for major CV events ($P < 0.001$) and 36% relative (10% absolute) reduction in all-cause deaths ($P < 0.001$).[357]

Implantable cardioverter defibrillators

- Implantation of an implantable cardioverter defibrillator (ICD) in combination with bi-ventricular pacing can be considered in patients who remain symptomatic

with severe heart failure NYHA class III–IV with LVEF $\leq$ 35% and QRS duration >120 ms to improve morbidity or mortality (Class of recommendation IIa, level of evidence B).
- ICD therapy is recommended to improve survival in patients who have survived cardiac arrest or who have sustained ventricular tachycardia, which is either poorly tolerated or associated with reduced systolic left ventricular function (Class of recommendation I, level of evidence A).
- ICD implantation is reasonable in selected symptomatic patients with LVEF <30–35%, not within 40 days of a myocardial infarction, on optimal background therapy including ACE-inhibitor, ARB, beta-blocker, and an aldosterone antagonist, where appropriate, to reduce sudden death (Class of recommendation I, level of evidence A).

In patients with documented sustained ventricular tachycardia or ventricular fibrillation, the ICD is highly effective in treating recurrences of these arrhythmias, either by anti-tachycardia pacing or cardioversion/defibrillation, thereby reducing morbidity and the need for rehospitalization.

The ICD is effective in patients at high risk of sudden death, i.e. with a history of myocardial infarction and reduced systolic left ventricular function.[295] In the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II), 1232 patients with a myocardial infarction >1 month earlier and a LVEF of <30%, were randomized to an ICD or not and followed for 4.5 years.[296] The trial was stopped prematurely by the Safety Committee when pre-specified stopping boundaries had been crossed. Mean follow-up was 20 month and there were 202 deaths in the trial. Allocation to ICD therapy was associated with a 31% relative (6% absolute) risk reduction of mortality ($P = 0.016$). In DEFINITE, patients with non-ischaemic cardiomyopathy were randomized to ICD or control. No significant effect on all-cause mortality was seen but sudden death was reduced significantly.[297] Although these trials did include a large percentage of patients with a history of heart failure, they did not address specifically, the role of ICD in heart failure patients in general. The selection citeria, the limited follow-up in MADIT II (20 months), increased morbidity with ICD and the low cost-effectiveness make it inappropriate to extend the findings into a general population with CHF. The COMPANION trial included patients with left ventricular systolic dysfunction, wide QRS complex suggesting dyssynchrony and heart failure and showed that implantation of an ICD in combination with resynchronization in patients with severe heart failure reduced mortality and morbidity (See under Resynchronization).[291] However, CRT-D was not superior to CRT alone in terms of reducing mortality and therefore the treatment associated with lower morbidity and cost may be preferred for the majority of patients. CRT-D should be reserved for patients considered at very high risk of sudden death despite medical treatment and CRT alone. The cost-effectiveness of this treatment needs to be established.[298] In the SCD-HeFT trial, 2521 patients with CHF and LVEF $\leq$ 35% were randomized to placebo, amiodarone or single-lead ICD implantation. After a median follow-up of 45.5 months, there was a significant reduction in mortality by ICD therapy: HR 0.77 (97.5% CI: 0.62–0.96; $P = 0.007$).[269] There was no difference between placebo and amiodarone on survival.

Several recent meta-analyses estimated the effect of ICD implantation on all-cause mortality in symptomatic patients with reduced ejection fraction.[262,299,300] Nanthakumar reported a significant reduction in mortality with ICD implantation ($n = 1623$) HR 0.75 (95% CI: 0.63–0.91; $P = 0.003$). No subgroups including age were analysed. Desai *et al.* focused their meta-analysis on studies including heart failure of non-ischaemic aetiology including 1854 patients in trials on primary prevention. They found that ICD treatment reduced all-cause mortality in this patient group (RR 0.69; 95% CI: 0.55–0.87; $P = 0.002$). Cleland *et al.* excluded two trials (MUSTT and COMPANION) because of different trial designs in these studies but their findings were consistent with the others. As the effectiveness with ICD is time-dependent,[301] the anticipated duration of treatment is important to establish cost-effectiveness. Accordingly, the age of the patient and non-cardiac comorbidity must also be taken into account. Treatment of patients in NYHA class IV is not well established unless associated with CRT in the context of dyssynchrony. There is no evidence that patients with DCM obtain proportionally less benefit but as the prognosis of this group is general better, the absolute benefits may be less.[262]

Radiofrequency catheter ablation

Catheter ablation may be indicated in patients with heart failure and reciprocating tachycardias. However, there are insufficient data on the role of ablation on sustained ventricular tachycardias in patients with heart failure or selected patients with AF. It may be an adjunctive therapy to ICDs in some patients.

Heart replacement therapies: heart transplantation, ventricular assist devices, and artificial heart

Heart transplantation

- Heart transplantation is an accepted mode of treatment for end stage heart failure. Although controlled trials have never been conducted, it is considered to significantly increase survival, exercise capacity, return to work and quality of life compared with conventional treatment, provided proper selection criteria are applied (Class of recommendation I, level of evidence C).

Recent results in patients on triple immunosuppressive therapy have shown a 5-year survival of ~70–80%[302] and return to full-time or part-time work, or seeking employment after 1 year in about two-third of the patients in the best series.[303]

Combined treatment with ACE-inhibitors and beta-blockers has markedly improved outcome and quality of life for patients with severe heart failure to the extent that a significant number of patients are now being withdrawn from the transplant waiting list.

Patients who should be considered for heart transplantation are those with severe heart failure with no alternative form of treatment. Predictors of poor survival are taken into account. However, the introduction of new treatments has probably modified the prognostic significance of the variables traditionally used to identify heart transplant candidates i.e. VO_2 max (see prognostication page 14). The patient must be willing and capable to undergo intensive medical treatment, and be emotionally stable so as to withstand the many uncertainties likely to occur both before and after transplantation. The contraindications for heart transplantation are shown in *Table 21*.

Besides shortage of donor hearts, the main problem of heart transplantation is rejection of the allograft, which is responsible for a considerable percentage of deaths in the first post-operative year. The long-term outcome is limited predominantly by the consequences of immuno-suppression (infection, hypertension, renal failure, malignancy, and by transplant coronary vascular disease).[304]

Ventricular assist devices and artificial heart

- Current indications for ventricular assist devices and artificial heart include bridging to transplantation, acute severe myocarditis, and in some permanent haemodynamic support (Class of recommendation IIa, level of evidence C).

At present, bi-ventricular support is only possible with external blood pumps. This approach is of limited duration due to infectious complications and is therefore used for short-term bridging (months) until cardiac transplantation.

Left ventricular assist devices[305] are being implanted in increasing numbers of heart failure patients. As the majority of these patients would fulfil criteria for heart transplantation, the methodology is used as a bridge for transplantation. However, due to the scarcity of donor organs, there are many patients now with duration of support of >1 year.

Indications for patients beyond those fulfilling the criteria for heart transplantation may be possible in the future, and first small clinical series with implantation of such univentricular devices as destination therapy are being released. Complications are mainly of infectious or thromboembolic nature and would currently limit broader application of this technology as long-term implants.[305] Fully implantable devices including those with rotational pumps are now being tested in clinical trials.

Ultrafiltration

- Ultrafiltration has been used for patients with pulmonary or peripheral oedema and/or severe congestive heart failure refractory to diuretics.

Ultrafiltration can resolve pulmonary oedema and overhydration in case of refractoriness to pharmacological therapies.[306] In most patients with severe disease the relief is temporary.[307]

Table 21 Contraindications for heart transplantation

- Present alcohol and/or drug abuse
- Lack of co-operation
- Serious mental disease, which could not be properly controlled
- Treated cancer with remission and <5 years follow-up
- Systemic disease with multi-organ involvement
- Uncontrolled infection
- Severe renal failure (creatinine clearance <50 mL/min) or creatinine >250 μmol/L
- Fixed high pulmonary vascular resistance
- Recent thrombo embolic complication
- Unhealed peptic ulcer
- Evidence of significant liver impairment
- Other diseases with a poor prognosis

Choice and timing of pharmacological therapy

The choice of pharmacological therapy in the various stages of heart failure that is caused by systolic dysfunction is displayed in *Table 22*. Before initiating therapy, the correct diagnosis needs to be established and considerations should be given to the Management Outline presented in *Table 6* (page 14).

European surveys on pharmacological therapy in primary care[308] and in hospital[11] have shown that ACE-inhibitors, beta-blockers, and in particular their combination, are not used as commonly as would be optimal.

Asymptomatic systolic left ventricular dysfunction

In general, the lower the ejection fraction, the higher the risk of developing heart failure. Treatment with an ACE-inhibitor is recommended in patients with reduced systolic function if indicated by a substantial reduction in LVEF (see section on imaging in the Diagnosis section) (recommendation page 3).

Beta-blockers should be added to the therapy in patients with asymptomatic left ventricular dysfunction following an acute myocardial infarction (recommendation page 33).

Symptomatic systolic left ventricular dysfunction: heart failure NYHA class II (*Figure 3*)

The diagnosis should be reviewed periodically to ensure that additional or alternative problems such as ischaemia, arrhythmias, or valve disease are not making an important contribution to symptoms.

Without signs of fluid retention

ACE-inhibitor (recommendation page 20). Titrate to the target dose used in large controlled trials (*Table 12*). Add a beta-blocker (recommendation page 23) and titrate to target dosages used in large controlled trials (*Table 18*).

With signs of fluid retention

Diuretics in combination with an ACE-inhibitor followed by a beta-blocker.

First, the ACE-inhibitor and diuretic should be co-administered. When symptomatic improvement occurs (i.e. fluid retention disappears), the optimal dose of the ACE-inhibitor should be maintained followed by a

Table 22 CHF—choice of pharmacological therapy in left ventricular systolic dysfunction

	ACE-inhibitor	Angiotensin receptor blocker	Diuretic	Beta-blocker	Aldosterone antagonists	Cardiac glycosides
Asymptomatic LV dysfunction	Indicated	If ACE intolerant	Not indicated	Post MI	Recent MI	With atrial fibrillation
Symptomatic HF (NYHA II)	Indicated	Indicated with or without ACE-inhibitor	Indicated if fluid retention	Indicated	Recent MI	(a) when atrial fibrillation (b) when improved from more severe HF in sinus rhythm
Worsening HF (NYHA III–IV)	Indicated	Indicated with or without ACE-inhibitor	Indicated, combination of diuretics	Indicated (under specialist care)	Indicated	Indicated
End-stage HF (NYHA IV)	Indicated	Indicated with or without ACE-inhibitor	Indicated, combination of diuretics	Indicated (under specialist care)	Indicated	Indicated

beta-blocker. The dose of diuretic can be adjusted based on patient stability. To avoid hyperkalaemia, any potassium-sparing diuretic should be omitted from the diuretic regimen before introducing an ACE-inhibitor. However, an aldosteronantagonist may be added if hypokalaemia persists. Add a beta-blocker and titrate to target dosages used in large controlled trials (*Table 18*). Patients in sinus rhythm receiving cardiac glycosides and who have improved from severe to mild heart failure should continue cardiac glycoside therapy (recommendation page 26). In patients who remain symptomatic and in patients who deteriorate, the addition of an ARB should be considered (recommendation page 24).

Worsening heart failure (*Figure 4*)

Frequent causes of worsening heart failure are shown in *Table 23*. Patients in NYHA class III that have improved from NYHA class IV during the preceding 6 months or are currently NYHA class IV should receive low-dose spironolactone (12.5–50 mg daily recommendation page 24). Cardiac glycosides are often added. Loop diuretics can be increased in dose, and combinations of diuretics (a loop diuretic with a thiazide) are often helpful.

Consider heart transplantation or reconsider any benefit that might be derived from coronary revascularization procedures, aneurysmectory, valve surgery, or resynchronisation therapy.

End-stage heart failure (patients who persist in NYHA IV despite optimal treatment and proper diagnosis

Patients should be (re)considered for heart transplantation. In addition to the pharmacological treatments outlined in the earlier sections, temporary inotropic support (intravenous sympathomimetic agents, dopaminergic agonists, and/or phosphodiesterase agents) can be used in end-stage heart failure, but always should be considered as an interim approach to further treatment that will benefit the patient.

For patients on the waiting list for transplantation bridging procedures, circulatory support with intra-aortic balloon pumping or ventricular assist devices, haemofiltration or dialysis may sometimes be necessary. These should be used only in the context of a strategic plan for the long-term management of the patient with special focus on end-organ function in order to achieve the maximum benefit from heart replacement.

Palliative treatment in terminal patients should always be considered and may include the use of opiates for the relief of symptoms.

Management of heart failure because of preserved left ventricular ejection fraction

There is still little evidence from clinical trials or observational studies on how to treat PLVEF. Further, much debate prevails about the prevalence of heart failure that is due to pure diastolic dysfunction. Although recent epidemiological studies suggest that in the elderly the percentage of patients hospitalized with heart failure-like symptoms and PLVEF may be as high as 35–45%, there is uncertainty about the prevalence of diastolic dysfunction in patients with heart failure symptoms and a normal systolic function in the community.

Heart failure with PLVEF and heart failure because of diastolic dysfunction are not synonymous. The former diagnosis implies the evidence of preserved LVEF and not the demonstration of left ventricular diastolic dysfunction.

The diagnosis of isolated diastolic heart failure also requires evidence of abnormal diastolic function, which may be difficult to assess in atrial fibrillation.

Causes of heart failure because of diastolic dysfunction include myocardial ischaemia, hypertension, myocardial hypertrophy, and myocardial/pericardial constriction. These causes should be identified and treated appropriately.

Precipitating factors should be identified and corrected, in particular tachy-arrhythmias should be prevented and sinus rhythm restored whenever possible. Rate control is important. Treatment approach is similar to patients without heart failure.[309]

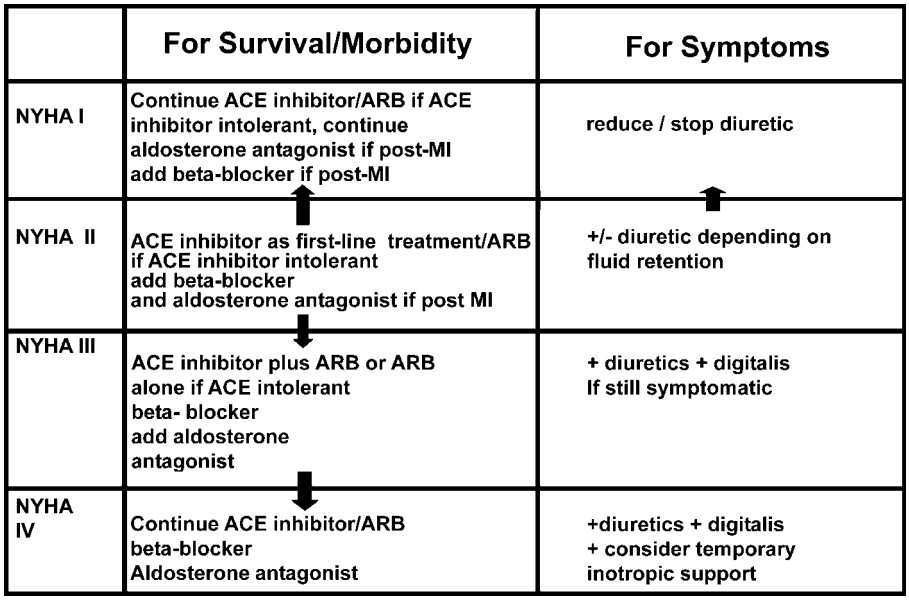

Figure 4 Pharmacological therapy of symptomatic CHF that is due to systolic left ventricular dysfunction. The algorithm should primarily be viewed as an example of how decisions on therapy can be made depending on the progression of heart failure severity. A patient in NYHA Class II can be followed with proposals of decision-making steps. Individual adjustments must be taken into consideration.

Table 23 Most frequent causes of worsening heart failure

Non-cardiac
- Non-compliance to the prescribed regimen (salt, liquid, medication)
- Recently co-prescribed drugs (anti-arrhythmics other than amiodarone, beta-blockers, NSAIDs, verapamil, diltiazem)
- Infection
- Alcohol abuse
- Renal dysfunction (excessive use of diuretics)
- Pulmonary embolism
- Hypertension
- Thyroid dysfunction (e.g. amiodarone)
- Anaemia

Cardiac
- Atrial fibrillation
- Other supraventricular or ventricular arrhythmias
- Bradycardia
- Myocardial ischaemia (frequently symptomless), including myocardial infarction
- Appearance or worsening of mitral or tricuspid regurgitation
- Excessive preload reduction (e.g. due to diuretics + ACE-inhibitors/nitrates)

Pharmacological therapy of heart failure with PLVEF or diastolic dysfunction

The recommendations provided below are largely speculative in that limited data exist in patients with PLVEF or diastolic dysfunction (Class of recommendation IIa, level of evidence C); the reason for the sparsity of data is that patients are excluded from nearly all large controlled trials in heart failure.

Presently, we do not have clear evidence that patients with primary diastolic heart failure benefit from any specific drug regimen. Some evidence is available indicating that patients with heart failure and preserved LVEF benefit from digoxin in the DIG study[238] in a composite of death or hospitalizations for heart failure. Inhibition of the renin angiotensin system with candesartan in CHARM Preserved[310] reduced cardiovascular mortality or hospitalizations for heart failure slightly and heart failure hospitalizations significantly; mortality, on the other hand, was not influenced. In these studies, however, there was no objective measure of diastolic function and, by consequence, do not permit any conclusion about treatment of diastolic function in general. Because heart failure is most often due to coronary artery disease and/or hypertension, it is most logical to search for these conditions by appropriate tests and then to treat the patients according to general principles for managing these disorders.

(1) ACE-inhibitors may improve relaxation and cardiac distensibility directly and may have long-term effects through their anti-hypertensive effects and regression of hypertrophy and fibrosis.
(2) Diuretics may be necessary when episodes with fluid overload are present, but should be used cautiously so as not to lower preload excessively and thereby reduce stroke volume and cardiac output.
(3) Beta-blockade could be instituted to lower heart rate and increase the diastolic period.
(4) Verapamil-type calcium antagonists may be used for the same reason.[311] Some studies with verapamil have shown a functional improvement in patients with hypertrophic cardiomyopathy.[312]

(5) A high dose of an ARB may reduce hospitalizations.[310]

In general, the treatment of PLVEF/diastolic dysfunction remains difficult and often unsatisfactory. One of the main problems is that isolated diastolic dysfunction may be rare, the condition often occurring in conjunction with some degree of systolic dysfunction. As conditions under which PLVEF/diastolic dysfunction occur vary between patients and no controlled data from studies exist, straightforward therapeutic algorithms are not easy to provide for the individual.

Heart failure treatment in the elderly

Heart failure occurs predominantly among elderly patients with a median age of about 75 years in community studies. Ageing is frequently associated with co-morbidity. Frequent concomitant diseases are hypertension, renal failure, obstructive lung disease, diabetes, stroke, arthritis, and anaemia. Such patients also receive multiple drugs, which includes the risk of unwanted interactions and may reduce compliance. In general, these patients have been excluded from randomized trials. In addition, elderly patients with heart failure have reduced cognitive function compared with healthy individuals.[313] Accordingly, the approach to the elderly patient with heart failure must include the understanding of several associated conditions in the therapeutic decision.

The therapeutic approach to systolic dysfunction in the elderly should be principally identical to that in younger heart failure patients on the choice of drug treatment. Altered pharmacokinetic and pharmacodynamic properties of cardiovascular drugs in the elderly necessitate that therapy should be applied more cautiously. Sometimes reduced dosages are necessary.

Renal dysfunction is of special importance because some cardiovascular drugs that are used frequently, such as most ACE-inhibitors and digoxin, are excreted in active form in the urine (for calculating the creatinine clearance, see *Table 3*, Diagnosis section).

Other complicating factors include diastolic dysfunction, blunting of baroreceptor function, and orthostatic dysregulation of blood pressure.

A sedentary lifestyle with deconditioning and reduced skeletal mass, as well as changes in nutritional habits leading to reduced calorie/protein intake are further complicating factors in the management of elderly heart failure patients.

ACE-inhibitors and ARBs

ACE-inhibitors and ARBs are effective and well tolerated in elderly patients in general. Because of a greater likelihood for hypotension and a delayed excretion rate of most ACE-inhibitors, low-dose titration is advisable. Initiation of ACE-inhibitor/ARBs therapy should be supervised, if possible, with monitoring of supine and standing blood pressure, renal function, and serum potassium levels. With such precautions, treatment can be introduced in the outpatient setting.

Diuretic therapy

In the elderly, thiazides are often ineffective because of reduced glomerular filtration rate. Reduced absorption rate and bio-availability of drugs or an increased excretion rate of thiazides or loop diuretics may lead to delayed onset, prolonged duration or sometimes reduced drug action. On the other hand, diuretics often cause orthostatic hypotension and/or further reduction in renal function. In elderly patients, hyperkalaemia is more frequently seen with a combination of aldosterone antagonsist and ACE-inhibitors or NSAIDs and coxibs.

Beta-blockers

Beta-blocking agents are surprisingly well tolerated in the elderly if patients with such contraindications as sinoatrial disease, AV-block and obstructive lung disease are excluded. Currently used beta-blockers in heart failure are eliminated by hepatic metabolism and do not require dosage reduction in patients with decreased renal function. Initiation of beta-blockade, however, should be carried out with low dosages and prolonged periods of titration. Beta-blockade should not be withheld because of increasing age alone.

Cardiac glycosides

Elderly patients may be more susceptible to adverse effects of digoxin. This glycoside is mainly eliminated in active form by the kidney and therefore half-lives increase up to two- to three-fold in patients aged over 70 years. Initially, low dosages are recommended in patients with elevated serum creatinine.

Vasodilator agents

Venodilating drugs, such as nitrates and the arterial dilator hydralazine and the combination of these drugs, should be administered carefully because of the risk of hypotension.

Little data exist concerning the efficacy and safety of these agents in the treatment of elderly heart failure patients.

Arrhythmias

- In the approach to arrhythmia, it is essential to recognize and correct precipitating factors, improve cardiac function and reduce neuroendocrine activation with beta-blockade, ACE-inhibition, and possibly, aldosterone receptor antagonists (Class of recommendation I, level of evidence C, class I).

Both supraventricular and ventricular arrhythmias occur frequently in heart failure. Sudden death accounts for ~40–50% of all deaths, decreasing in relative proportion in advancing stages of heart failure.[314] Various mechanisms, i.e. structural cardiac changes, myocardial ischaemia and neurohormonal activation, may play a role. Further precipitating factors for arrhythmias include electrolyte disturbances (hypokalaemia, hypomagnesaemia, and hyperkalaemia), drug interaction with cardiac pump function or electrical stability, such as some calcium antagonists and some anti-arrhythmic

agents, digitalis toxicity, and inter-current diseases (e.g. hyperthyroidism and respiratory diseases).

Ventricular arrhythmias

- In patients with ventricular arrhythmias, the use of anti-arrhythmic agents is only justified in patients with severe, symptomatic, ventricular tachycardias and where amiodarone should be the preferred agent (Class of recommendation IIa, level of evidence B).[266,268]
- The routine use of anti-arrhythmic agents for asymptomatic premature ventricular complexes or non-sustained ventricular tachycardias is not justified (see section Anti-arrhythmics, page 28).
- ICD implantation is indicated in patients with heart failure and life threatening ventricular arrhythmias (i.e. ventricular fibrillation or sustained ventricular tachycardia) and in selected patients at high risk of sudden death (Class of recommendation I, level of evidence A).[295,296,315,316]

Atrial fibrillation

- For persistent (non-self-terminating) atrial fibrillation, electrical cardioversion could be considered, although its success rate may depend on the duration of atrial fibrillation and left atrial size (Class of recommendation IIa, level of evidence B).
- In patients with atrial fibrillation and heart failure and/or depressed left ventricular function, the use of anti-arrhythmic therapy to maintain sinus rhythm should be restricted to amiodarone (Class of recommendation I, level of evidence C) and, if available, to dofetilide (Class of recommendation IIa, level of evidence B).[270]
- In asymptomatic patients beta-blockade, digitalis glycosides or the combination may be considered for control of ventricular rate (Class of recommendation I, level of evidence B). In symptomatic patients with systolic dysfunction digitalis glycosides are the first choice (Class of recommendation IIa, level of evidence C). In PLVEF verapamil can be considered (Class of recommendation IIa, level of evidence C).
- Anti-coagulation in persistent atrial fibrillation with warfarin should always be considered unless contraindicated (Class of recommendation I, level of evidence C).
- Management of acute atrial fibrillation is not dependent on previous heart failure or not. Treatment strategy is dependent on symptoms and haemodynamic stability.[309]

There is no evidence in patients with persistent atrial fibrillation and heart failure that restoring and maintaining sinus rhythm is superior to control of heart rate, particularly in severe heart failure.[317,318] The development of atrial fibrillation in CHF is associated with worse prognosis.[319,320]

Amiodarone may convert atrial fibrillation to sinus rhythm and improve the success rate of electrical cardioversion.

In permanent atrial fibrillation, (cardioversion not attempted or failed) rate control is most important (Class of recommendation IIa, level of evidence C). If digoxin or warfarin is used in combination with amiodarone, their dosages may need to be adapted.

Symptomatic systolic left ventricular dysfunction and concomitant angina or hypertension

Specific recommendations in addition to general treatment for heart failure because of systolic left ventricular dysfunction.

If angina is present

(i) optimize existing therapy, e.g. beta-blockade;
(ii) add long-acting nitrates;
(iii) add amlodipine or felodipine, if not successful;
(iv) consider coronary revascularization

If hypertension is present

(i) optimize the dose of ACE-inhibitors, beta-blocking agents, and diuretics;
(ii) add spironolactone or ARBs if not present already;
(iii) try second generation dihydropyridine derivatives if not successful.

Care and follow-up (*Table 24*)

- An organized system of specialist heart failure care improves symptoms and reduces hospitalizations (Class of recommendation I, level of evidence A) and mortality (Class of recommendation IIa, level of evidence B) of patients with heart failure.

Randomized controlled trials have generally demonstrated that a structured system of care improves outcomes, including quality of life, the frequency and duration of follow-up and survival.[232,321–325] However, some studies have failed to show benefit.[326–329] Various models have been tested (heart failure clinics, nurse-led home visits and/or telephone follow-up, multi-disciplinary care, extended home care services, and telemonitoring). It is not clear which model is superior. Most successful models have been based on the development of heart failure nurse specialists, which appears cost-

Table 24 Recommended components of care and following programmes (Class of recommendation I, level of evidence C)

• Use a multi-disciplinary team approach
• Vigilant follow-up, first follow-up within 10 days of discharge
• Discharge planning
• Increased access to health care
• Optimizing medical therapy with guidelines
• Early attention to signs and symptoms (e.g. telemonitoring)
• Flexible diuretic regimen
• Intense education and counseling
• Inpatient and outpatient (home-based)
• Attention to behavioural strategies
• Address barriers to compliance

effective.[323] It is likely that the optimal model will depend on local circumstances and resources and whether the model is designed for specific sub-groups of patients (e.g. severity of heart failure, age, co-morbidity, and left ventricular systolic dysfunction) or the whole heart failure population.

Unplanned re-admission of patients with heart failure is related to medical complications (e.g. uncontrolled hypertension, infections, anaemia, and renal dysfunction), environmental factors (e.g. failing social support), behavioural factors (e.g. non-compliance with drugs, diet, or other lifestyle modifications) or to factors related to discharge planning (e.g. premature discharge, inadequate treatment, or patient education and poor follow-up).[330]

Although basic agreement can be achieved on the content of care needed by patients with heart failure (e.g. all patients should be properly counselled, see page 17), the organization should be closely adapted to the needs of the patient group and the resources of the organization. Depending on the local health care system, it seems important to determine which health care provider is the most appropriate to participate in various components. Nurses and other health care providers can play an important role in these innovative forms of care.

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