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ESC Guidelines

Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005)

The Task Force for the Diagnosis and Treatment of Chronic Heart Failure 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.

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 tables on page 3.

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 while 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. Within this Task Force, statements of Conflicts of Interests were collected, which are available at the ESC Office. The draft was sent to the Committee and the document reviewers (see title page) and after their input the document was updated, reviewed and then approved for presentation. The summary is based on a full document, which includes more background statements and includes references. This document is available at the ESC website www.escardio.org. The full report should be used when in doubt or when further information is required. An evidenced 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.

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

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.

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. There are also patients with myocardial systolic dysfunction without symptoms of heart failure and who constitute approximately a similar prevalence.[5–7] 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.[8,9] Many patients with heart failure have symptoms and PLVEF.[10]

Studies show that the accuracy of diagnosis by clinical means alone is often inadequate,[11,12] 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 *de novo* AHF or decompensation of chronic heart failure (CHF) characterized by signs of pulmonary congestion, including pulmonary oedema. Other forms include hypertensive AHF, pulmonary oedema, cardiogenic shock, high output failure, and right heart failure. (See Guidelines on acute heart failure.[13])

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

The present document will concentrate on the syndrome of CHF and leave out aspects on AHF.[13] Thus, heart failure, if not stated otherwise, is referring to the chronic state.

Systolic vs. diastolic heart failure

Most heart failures are associated with evidence of left ventricular systolic dysfunction, although diastolic impairment at rest is a common if not universal accompaniment. In most cases, diastolic and systolic heart failures should not be considered as separate pathophysiological entities. 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.[10,14]

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 other descriptive terms still in occasional use; the clinical utility of these terms is descriptive without etiological 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 dyspnea or fatigue, severe for patients who are markedly symptomatic and need frequent medical attention and moderate for the remaining patient cohort.

Definition of chronic heart failure

- Heart failure should never be the only diagnosis.

Many definitions of CHF exist[15–18] but highlight only selective features of this complex syndrome. The diagnosis of heart failure relies on clinical judgement based on a history, physical examination, and appropriate investigations.

Heart failure is 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*). The distinctions between cardiac dysfunction, persistent heart failure, heart failure that has been rendered asymptomatic by therapy, and transient heart failure are outlined in *Figure 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 or nitrate administration).

Asymptomatic left ventricular systolic dysfunction is considered as precursor of symptomatic CHF and is

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.

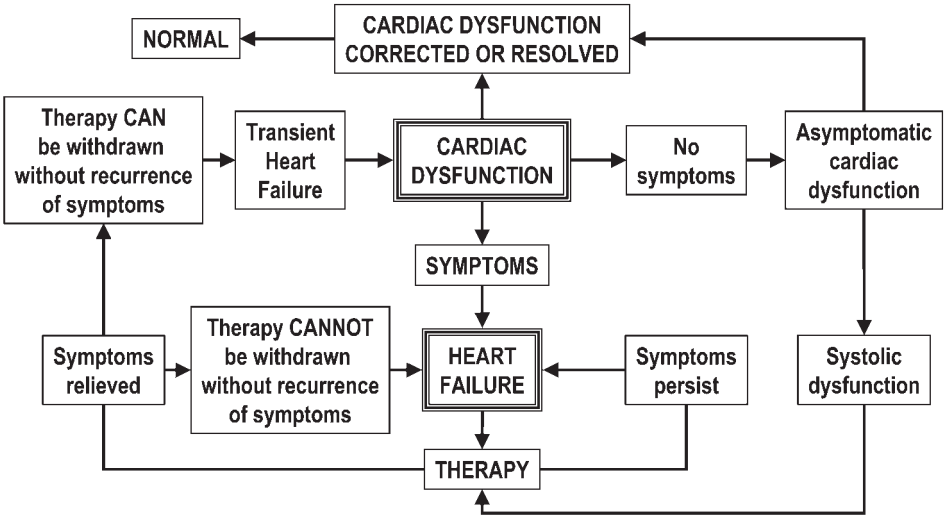

Figure 1 Relationship between cardiac dysfunction, heart failure, and heart failure rendered asymptomatic.

associated with high mortality.[19] It is important when diagnosed and treatment is available, and the condition is therefore included in these Guidelines.

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.[20,21] This suggests either that raised pulmonary capillary pressure is not the only factor responsible for exertional breathlessness (e.g. lungwater and plasma albumin) or that current techniques to measure true pulmonary capillary pressure may not be adequate. Variation in the degree of mitral regurgitation will also influence breathlessness.

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, in obese, and in women. It should be interpreted carefully and different modes (e.g. effort and nocturnal) should be assessed.

Fatigue is also an essential symptom in heart failure. The origins of fatigue are complex including low cardiac output, peripheral hypoperfusion, skeletal muscle deconditioning, and confounded by difficulties in quantifying this symptom.

Peripheral oedema, raised venous pressure, and hepatomegaly are the characteristic signs of congestion of systemic veins.[22,23] Clinical signs of heart failure should be assessed in a careful clinical examination, including observing, palpating, and auscultating the patient.

Symptoms and the severity of heart failure

- There is a poor relationship between symptoms and the severity of cardiac dysfunction.[10,24] However, symptoms may be related to prognosis particularly if persisting after therapy.[25]

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. However, as noted subsequently, symptoms cannot guide the optimal titration of neurohormonal blockers. The New York Heart Association (NYHA) classification is in widespread use (*Table 2*). In other situations, the classification of symptoms into mild, moderate, or severe is used. Patients in NYHA class I 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.

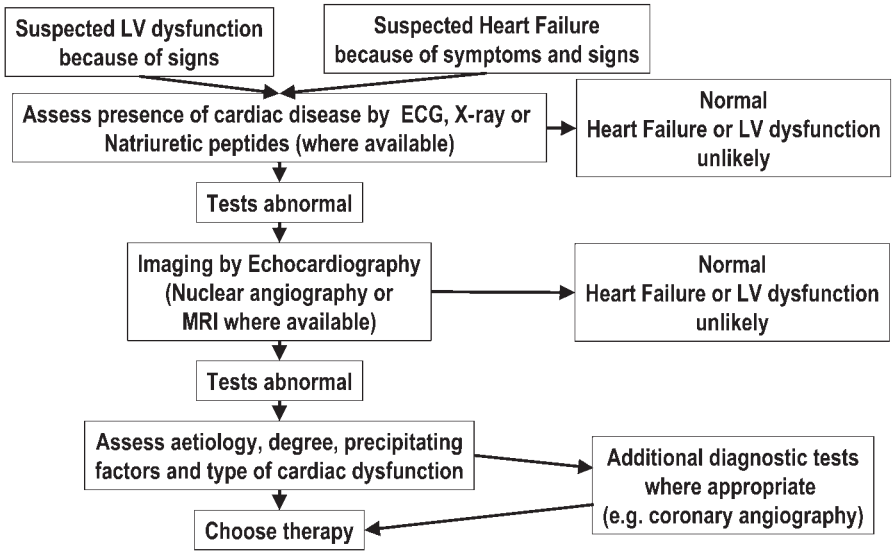

Figure 2 Algorithm for the diagnosis of heart failure or left ventricular dysfunction.

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

In acute myocardial infarction, the classification described by Killip[26] has been used to describe symptoms and signs.[27] 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.[28] Mild symptoms should not be equated with minor cardiac dysfunction.

Electrocardiogram

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

Electrocardiographic changes are common in patients suspected of having heart failure whether or not the diagnosis proves to be correct. An abnormal ECG, therefore, has little predictive value for the presence of heart failure. On the other hand, if the ECG is completely normal, heart failure, especially due LV systolic dysfunction, is unlikely. The presence of pathological Q-waves may suggest myocardial infarction as the cause of cardiac dysfunction. A QRS width $>$120 ms suggests that cardiac dyssynchrony may be present and a target for treatment.

The chest X-ray

- Chest X-ray should be part of the initial diagnostic work-up in heart failure. It is useful to detect cardiomegaly and pulmonary congestion; however, it has only predictive value in the context of typical signs and symptoms and in abnormal ECG.

Haematology and biochemistry

Routine diagnostic evaluation of patients with CHF includes: complete blood count (Hb, leukocytes, and platelets), S-electrolytes, S-creatinine, S-glucose, S-hepatic enzymes, and urinalysis. Additional tests to evaluate thyroid function should be considered according to clinical findings. In acute exacerbations, acute myocardial infarction is excluded by myocardial specific enzyme analysis.

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 as the cause of symptoms.
- BNP and NT-proBNP have considerable prognostic potential, although evaluation of their role in treatment monitoring remains to be determined.

As the diagnostic potential of natriuretic peptides is less clear cut when systolic function is normal, there is increasing evidence that their elevation can indicate diastolic dysfunction is present.[29,30] Other common cardiac abnormalities that may cause elevated natriuretic peptide levels include left ventricular hypertrophy, valvular heart disease, acute or chronic ischaemia or hypertension,[31] and pulmonary embolism.[32]

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.

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 suggest 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.[33]

Echocardiography

- Echocardiography is the preferred method for the documentation of cardiac dysfunction at rest.
- The most important measurement of ventricular function is the left ventricular ejection fraction (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.

Assessment of LV diastolic function

Assessment of diastolic function may be clinically useful: (1) to detect abnormalities of diastolic function in patients who present with CHF and normal left ventricular ejection fraction, (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

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.[34] Furthermore, it is essential to exclude pulmonary disease.[35]

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.[36]

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.[37]

The three filling patterns 'impaired relaxation', 'pseudonormalized filling', and 'restrictive filling' represent mild, moderate, and severe diastolic dysfunction, respectively[37] (*Figure 3*). 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. We still lack prospective outcome studies that investigate if assessment of diastolic function by these criteria may improve management of heart failure patients.

Transoesophageal echocardiography is not recommended routinely and can only be advocated in patients who have an inadequate echo window, in complicated valvular patients, and 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.

Additional non-invasive tests to be considered

In patients in whom 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 stress echocardiography, radionuclide imaging, and cardiac magnetic resonance imaging (CMR).

Cardiac magnetic resonance imaging (CMR)

- 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.[38,39] The method is well suited for detection of congenital defects, masses and tumours, valvular, and pericardial disease.

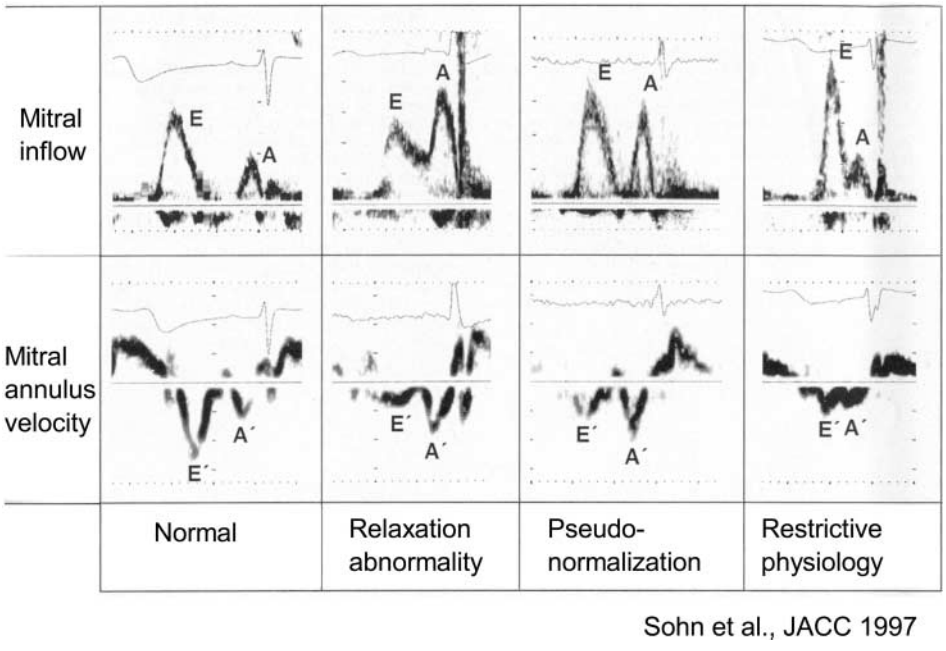

Figure 3 The three filling patterns 'impaired relaxation', 'pseudonormalised filling', and 'restrictive filling' represent mild, moderate, and severe diastolic dysfunction, respectively.[37]

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.

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.

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.

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. Revascularization has not been shown to alter prognosis in heart failure in clinical trials and therefore, in the absence of angina pectoris unresponsive to medical therapy, coronary arteriography is not indicated. 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. Routine right heart catheterization should not be used to tailor chronic therapy.

Tests of neuroendocrine evaluations other than natriuretic peptides

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

Holter electrocardiography: ambulatory ECG and long-time ECG recording (LTER)

- 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. Recording LTER should be restricted to patients with CHF and symptoms suggestive of an arrhythmia.

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 3*). 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 4*) should be performed or re-evaluated in cases in which diagnostic doubt persists or clinical features suggest a reversible cause for heart failure.

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 5* provides a management outline connecting the diagnosis component of the guidelines with the treatment section.

Prognostication

- 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 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 6*.

Treatment of heart failure

Aims of treatment in heart failure

(i) Prevention—a primary objective
   a. Prevention and/or controlling of diseases leading to cardiac dysfunction and heart failure.
   b. Prevention of progression to heart failure once cardiac dysfunction is established.

Table 3 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 4 Additional tests to be considered to support the diagnosis or to suggest alternative diagnoses

Tests	Diagnosis of heart failure		Suggests alternative or additional diagnosis
	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.

(ii) Maintenance or improvement in quality of life
(iii) Improved survival

Prevention of heart failure

- The development of ventricular dysfunction and heart failure may be delayed or prevented by treatment of conditions leading to heart failure, in particular in patients with hypertension and/or coronary artery disease (Class of recommendation I, level of evidence A).[40]
- The prevention of heart failure should always be a primary objective.

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), providing the benefits of intervention outweigh the risks. When the underlying cause cannot be corrected treatment should be directed at delaying or preventing left ventricular dysfunction that will increase the risk of sudden death and the development of heart failure.

How to modulate progression from asymptomatic left ventricular dysfunction to heart failure is described on page 1133, Treatment of Asymptomatic Left Ventricular Dysfunction.

Management of chronic heart failure

The therapeutic approach in patients with CHF that is caused by left ventricular systolic dysfunction includes

Table 5 Management outline

Establish that the patient has heart failure (in accordance with the definition presented on page 1122, 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 1124, *Table* 6.
Assess complicating factors (e.g. renal dysfunction, arthritis)
Counsel patient and relatives
Choose appropriate management
Monitor progress and manage accordingly

general advice and other non-pharmacological measures, pharmacological therapy, mechanical devices, and surgery. The currently available types of management are outlined in *Tables 5* and *7*.

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.

Weight monitoring

Patients are advised to weigh 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 in weight is noted).

Dietary measures

Sodium. Controlling the amount of salt in the diet is a problem, that is, more important in advanced than in mild heart failure.

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

Alcohol. Moderate alcohol intake (one beer, 1–2 glasses of wine/day) is permitted other than in case of alcoholic cardiomyopathy when it is prohibited.

Table 6 Risk stratification in CHF predictors

Demographic and historical	Clinical	Electrophysiologic	Functional/exertional	Blood	Central haemodynamic
Advanced age*[123–125]	High heart rate[149]	Broad QRS[95,127]	VO_2 max* (mL/kg per min <10–14)[128–130]	High serum BNP*[31,131]	Low LVEF*[124,132–134]
Coronary aetiology[123,135]	Persistent low BP*[123]	Low heart rate variability[136,137]	High VE/VCO_2 ratio[138]	High serum norepinephrine[139,140]	Increased left ventricular volumes[141,142]
Diabetes[143]	NYHA functional Class III–IV*[123,124,144]	Complex ventricular rhythms [110,139]	Low 6 min walking ability[145,146]	Low serum sodium*[123,147]	Low cardiac index[123]
Resuscitated sudden death*[110]	Low body-mass index[148]	T-wave alternans[134]		High serum creatinine*[123,147,150]	High left ventricular filling pressure[123,124]
Race[126]	Ventilatory rhythm and rate disturbances[151,152]			High serum bilirubine*[147]	Restrictive mitral filling pattern[153,154]
				Anaemia[155]	Impaired right* ventricular function[156,157]
				High serum troponin[158]	Cardiothoracic ratio[139,159]
				High serum uric acid[160]	

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.

Table 7 Treatment options: general advice and measures, exercise and exercise training, pharmacological therapy, and devices and surgery

Non-pharmacological management
General advice and measures
Exercise and 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 (multi-site) pacing
Implantable cardioverter defibrillator (ICD)
Heart transplantation, ventricular assist devices, and artificial heart

Obesity
Treatment of CHF should include weight reduction in obese patients.

Abnormal weight loss
Clinical or subclinical malnutrition is present in ~50% of patients with severe CHF. The wasting of total body fat and lean body mass that accompanies weight loss is called cardiac cachexia. Cardiac cachexia is an important predictor of reduced survival.[41]

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 or very hot or humid places should be discouraged. In general, short air flights are preferable to long journeys by other means of transport.

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. Little is known 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. Immunization for influenza is widely used.

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

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:

(i) Non-steroidal anti-inflammatory drugs (NSAIDS) and coxibs
(ii) Class I anti-arrhythmic agents (page 1131)
(iii) Calcium antagonists (verapamil, diltiazem, and short-acting dihydropyridine derivatives (page 1126)
(iv) Tricyclic anti-depressants
(v) Corticosteroids
(vi) Lithium

Rest, exercise, and exercise training

Rest
In acute heart failure or destabilization of CHF, physical rest or bed rest is recommended.

Exercise
Exercise improves skeletal muscle function and therefore overall functional capacity. Patients should be encouraged and advised on how to carry out daily physical and leisure time activities that do not induce symptoms. Exercise training programs are encouraged in stable patients in NYHA class II–III. Standardized recommendations for exercise training in heart failure patients by the European Society of Cardiology have been published.[42]

Pharmacological therapy

Angiotensin-converting enzyme inhibitors

- Angiotensin-converting enzyme (ACE) inhibitors are recommended as first-line therapy in patients with a reduced left ventricular systolic function expressed as a subnormal ejection fraction, i.e. $<$40–45% with or without symptoms (see non-invasive imaging; page 1121 Diagnosis section) (Class of recommendation I, level of evidence A).
- ACE-inhibitors should be uptitrated 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 should be treated with an ACE-inhibitor to delay or prevent the development of heart failure. ACE-inhibitors also reduce the risk of

myocardial infarction and sudden death in this setting (Class of recommendation I, level of evidence A).[43–46]

ACE-inhibitors in symptomatic heart failure

- All patients with symptomatic heart failure that is caused by systolic left ventricular dysfunction should receive an ACE-inhibitor (Class of recommendation I, level of evidence A).[47]
- ACE-inhibition improves survival, symptoms, functional capacity, and reduces hospitalization in patients with moderate and severe heart failure and left ventricular systolic dysfunction.
- 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).[47,48]
- 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 and to reduce reinfarctions and hospitalizations for heart failure (Class of recommendation I, level of evidence A).[44,45,49]
- Asymptomatic patients with a documented left ventricular systolic dysfunction benefit from long-term ACE-inhibitor therapy (Class of recommendation I, level of evidence A).[43–46]
- Important adverse effects associated with ACE-inhibitors are cough, hypotension, renal insufficiency, hyperkalaemia, syncope, and angioedema. Angiotensin receptor blockers may be used as an effective alternative in patients who develop cough or angioedema on an ACE-inhibitor (Class of recommendation I, level of evidence A). Changes in systolic and diastolic blood pressure and increases in serum creatinine are usually small in normotensive patients.
- ACE-inhibitor treatment is contra-indicated in the presence of bilateral renal artery stenosis and angioedema during previous ACE-inhibitor therapy (Class of recommendation III, level of evidence A).

Target maintenance dose ranges of ACE-inhibitors shown to be effective in various trials are given in *Table 8*. Recommended initiating and maintenance dosages of ACE-inhibitors which have been approved for the treatment of heart failure in Europe are presented in *Table 9*.

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 10*.

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.

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).[50,51]
- 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 11 and 12*.

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). In patients who are unable to tolerate even low doses of aldosterone

Table 8 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[48]	Enalapril	20 mg b.i.d.	18.4 mg
V-HeFT II, 1991[161]	Enalapril	10 mg b.i.d.	15.0 mg
The SOLVD Investigators, 1991[162]	Enalapril	10 mg b.i.d.	16.6 mg
ATLAS, 1999[163]	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[44]	Captopril	50 mg t.i.d.	127 mg
AIRE, 1993[49]	Ramipril	5 mg b.i.d.	(not available)
TRACE, 1995[45]	Trandolapril	4 mg daily	(not available)

Table 9 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.

Table 10 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 (Level of Evidence C). 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 9*) and build-up to maintenance dosages shown to be effective in large trials (*Table 8*)
If renal function deteriorates substantially, stop treatment
Avoid potassium-sparing diuretics during initiation of therapy
Avoid NSAIDs and 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

antagonists due to hyperkalaemia and renal dysfunction, amiloride or triamterene may be used (Class of recommendation IIb, level of evidence C).
- Potassium supplements are generally ineffective in this situation (Class of recommendation III, level of evidence C).
- 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.

Table 11 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 diuretics and thiazides
With persistent fluid retention: administer loop diuretics twice daily
In severe heart failure add metolazone with frequent measurement of creatinine and electrolytes
Potassium-sparing diuretics: triamterene, amiloride and spironolactone
Use only if hypokalaemia persists after initiation of therapy with ACE, inhibitors and diuretics
Start one-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.

Beta-adrenoceptor antagonists

- Beta-blockers should be considered 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).[52–58]
- 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).[59]
- Differences in clinical effects may be present between different beta-blockers in patients with heart failure.[60,61] Accordingly, only bisoprolol, carvedilol, metoprolol succinate and nebivolol can be recommended (Class of recommendation I, level of evidence A).

Initiation of therapy

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.

Table 12 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		2.5		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

During titration, beta-blockers may reduce heart rate excessively, temporarily induce myocardial depression, and exacerbate symptoms of heart failure. *Table 13* gives the recommended procedure for the use of beta-blockers in clinical practice and contraindications.

Table 14 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) with systolic dysfunction to improve survival and morbidity (Class of recommendation I, level of evidence B).[62]
- Aldosterone antagonists are recommended in addition to ACE-inhibitors and beta-blockers 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).[63]

Administration and dosing considerations for aldosterone antagonists are provided in *Table 15*.

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).[64–67]
- 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 B).[68]
- 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) and hospital admissions for heart failure (Class of recommendation I, level of evidence A).[65,69–71,170]

In NYHA class III patients remaining symptomatic despite therapy with diuretics, ACE-inhibitors, and beta-blockers, there is no definite evidence for the recommendation of next addition; an ARB or an aldosterone antagonist to reduce further heart failure hospitalizations 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 (Class of recommendation I, level of evidence A).[65,68]

Dosing

Initiation and monitoring of ARBs, which are outlined in *Table 10*, are similar to procedures for ACE-inhibitors. Available ARBs and the recommended dose levels are shown in *Table 16*.

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).[72]
    - A combination of digoxin and beta-blockade appears superior to either agent alone in patients

Table 13 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 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

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. Asthma bronchiale
h. Severe bronchial disease
i. Symptomatic bradycardia or hypotension

Table 14 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[164]	1.25	2.5, 3.75, 5, 7.5, 10	10	Weeks–month
Metoprolol succinate CR[165]	12.5/25	25, 50, 100, 200	200	Weeks–month
Carvedilol[54]	3.125	6.25, 12.5, 25, 50	50	Weeks–month
Nebivolol[58]	1.25	2.5, 5, 10	10	Weeks–month

Daily frequency of administration as in the trials referenced here.

with atrial fibrillation (Class of recommendation IIa, level of evidence B).[73]
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).
- 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.

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).

Vasodilator agents in chronic heart failure

- There is no specific role for direct-acting vasodilator agents in the treatment of CHF (Class of recommendation III, level of evidence A) though they may be used as adjunctive therapy for angina or concomitant hypertension (Class of recommendation I, level of evidence A).

Hydralazine-isosorbide dinitrate

- In case of intolerance for ACE-inhibitors and ARBs, the combination hydralazine/nitrates can be tried to

Table 15 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

Table 16 Currently available angiotensin II receptor antagonists

Drug	Daily dose (mg)
Documented effects on mortality/morbidity	
Candesartan cilexetil[65]	4–32
Valsartan[67]	80–320
Also available	
Eprosartan[165]	400–800
Losartan[166,167]	50–100
Irbesartan[168]	150–300
Telmisartan[169]	40–80

reduce mortality and morbidity and improved quality of life (Class of recommendation IIa, level of evidence B).[74]

Nitrates

- Nitrates may be used for the treatment of concomitant angina or relief of dyspnoea. (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.

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).[75]

Calcium antagonists

- Calcium antagonists are not recommended for the treatment of heart failure caused by systolic dysfunction. 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).[76,77]
- Addition of newer calcium antagonists (felodipine and amlodipine) to standard treatment for heart failure does not improve symptoms and does not impact on survival (Class of recommendation III, level of evidence A).[76,77]

As long-term safety data with felodipine and amlodipine indicate a neutral effect on survival, they may offer a safe alternative for the treatment of concomitant arterial hypertension or angina not controlled by nitrates and beta-blockers.

Nesiritide

Nesiritide, a recombinant human brain or B-type natriuretic peptide (BNP), 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. Clinical experience with nesiritide is still limited. Nesiritide may cause hypotension and some patients are non-responders.

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.[13]
- Preliminary data suggests that some calcium sensitizers (e.g. levosimendan) may have beneficial effects on symptoms and end-organ function and are safe.[78]

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).[79]
- There is little evidence to show that anti-thrombotic therapy modifies the risk of death or vascular events in patients with heart failure.
- After a prior myocardial infarction, either aspirin or oral anti-coagulants are recommended as secondary prophylaxis (Class of recommendation IIa, level of evidence C).[80]
- Aspirin should be avoided in patients with recurrent hospitalization with worsening heart failure (Class of recommendation IIb, level of evidence B). Because of the potential for increased bleeding complications, anti-coagulant therapy should be administered under the most controlled conditions, planning monitoring in properly managed anti-coagulation clinics.

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. There is little evidence to support the concomitant treatment with an ACE-inhibitor and aspirin in heart failure.[81–83]

In general, 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), 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).[84]

Class II anti-arrhythmics

- Beta-blockers reduce sudden death in heart failure (Class of recommendation I, level of evidence A) (see also page 1127).[85] 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).[86]

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 and amiodarone is the preferred treatment in this condition.[87,88] 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).[89,90]

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).

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).

Revascularization

- There are no data from multicenter 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).

Mitral valve surgery

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

Left ventricular restoration

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).

Cardiomyoplasty

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

Partial left ventriculectomy (Batista operation)

- Partial left ventriculectomy cannot be recommended for the treatment of heart failure (Class of recommendation I, level of evidence C). Furthermore, the Batista operation should not be considered an alternative to heart transplantation (Class of recommendation III, level of evidence C).

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 IIb, level of evidence C).

Pacemakers

- 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 (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) and 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.[91–94] A beneficial effect on the composite of long-term mortality or all-cause hospitalization has recently been demonstrated, as well as a significant effect on mortality.[171]

Implantable cardioverter defibrillators

- Implantation of an implantable cardioverter defibrillators (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 $\geq$ 120 ms to improve mortality or morbidity (Class of recommendation IIa, level of evidence B).[93]
- 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).[95]
- ICD implantation is reasonable in selected 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).[90,96,97]

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 selection criteria, the limited follow-up and increased morbidity associated with ICD-implantation 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).[93] 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.[98] 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; $P = 0.007$).[90] 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.[83,99,100] As the effectiveness with ICD is time-dependent,[101] 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 generally better, the absolute benefits may be less.[83]

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).

Patients who should be considered for heart transplantation are those with severe symptoms of heart failure with no alternative form of treatment and with a poor prognosis. The introduction of new treatments has probably modified the prognostic significance of the variables traditionally used to identify heart transplant candidates i.e. VO2 max (see prognostication page 1122). 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

Table 17 Contraindications for heart transplantation

- Present alcohol and/or drug abuse
- Lack of proper 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, although some centres accept patients on haemodialysis
- Fixed high pulmonary vascular resistance (6–8 Wood units and mean transpulmonary gradient >15 mm Hg and pulmonary artery systolic pressure >60 mm Hg)
- Recent thrombo embolic complication
- Unhealed peptic ulcer
- Evidence of significant liver impairment
- Other disease with a poor prognosis

before and after transplantation. The contraindications for heart transplantation are shown in *Table 17*.

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 postoperative year. The long-term outcome is limited predominantly by the consequences of immunosuppression (infection, hypertension, renal failure, malignancy, and by transplant coronary vascular disease).[102]

Ventricular assist devices and artificial heart

- Current indications for left ventricular assist devices and artificial heart include bridging to transplantation, acute severe myocarditis, and in some patients permanent haemodynamic support (Class of recommendation IIa, level of evidence C).
- Left ventricular assist devices are being implanted as a bridge to transplantation. Experience from long-term treatment is accumulating but these devices are not recommended for routine long-term use (Class of recommendation IIb, level of evidence B).[103]

Ultrafiltration

- Ultrafiltration may be used to treat fluid overload (pulmonary or peripheral oedema) refractory to diuretics.[104] However, in most patients with severe heart failure, the relief is temporary.[105]

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 18*. Before initiating therapy, the correct diagnosis needs to be established and considerations should be given to the Management Outline presented in Table 5.

Asymptomatic left ventricular systolic dysfunction

In general, the lower the ejection fraction, the higher the risk of developing heart failure or sudden death. Treatment with an ACE-inhibitor is recommended in patients with reduced LVEF if indicated by a substantial reduction in LVEF (see section on echocardiography in the Diagnosis section) (recommendation page 1120).

Beta-blockers should be added to the therapy in patients with asymptomatic left ventricular dysfunction, especially if following an acute myocardial infarction (recommendation page 1127).

Symptomatic left ventricular systolic dysfunction: heart failure NYHA class II (*Figure 4*)

Without signs of fluid retention. ACE-inhibitor (recommendation page 1126). Titrate to the target dose used in large controlled trials (*Table 8*). Add a beta-blocker (recommendation page 1127) and titrate to target dosages used in large controlled trials (*Table 14*).

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 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 aldosterone antagonist may be added if hypokalaemia persists. Add a beta-blocker and titrate to target dosages used in large controlled trials (*Table 13*). Patients in sinus rhythm receiving cardiac glycosides and who have improved from severe to mild heart failure should continue cardiac glycoside therapy (recommendation page 1128) In patients who remain symptomatic and in patients who deteriorate, the addition of an ARB should be considered (recommendation page 1128).

Worsening heart failure (*Figure 3*)

Frequent causes of worsening heart failure are shown in *Table 19*. 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 1128). 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. Cardiac resynchronization therapy should be considered if there is evidence of left ventricular dyssynchrony. Heart transplantation, coronary revascularization, aneurysmectory, or valve surgery may play a limited role.

End-stage heart failure (patients who persist in NYHA IV despite optimal treatment and proper diagnosis (*Figure 4*)

Patients should be (re)considered for heart transplantation if appropriate. In addition to the pharmacological

Table 18 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

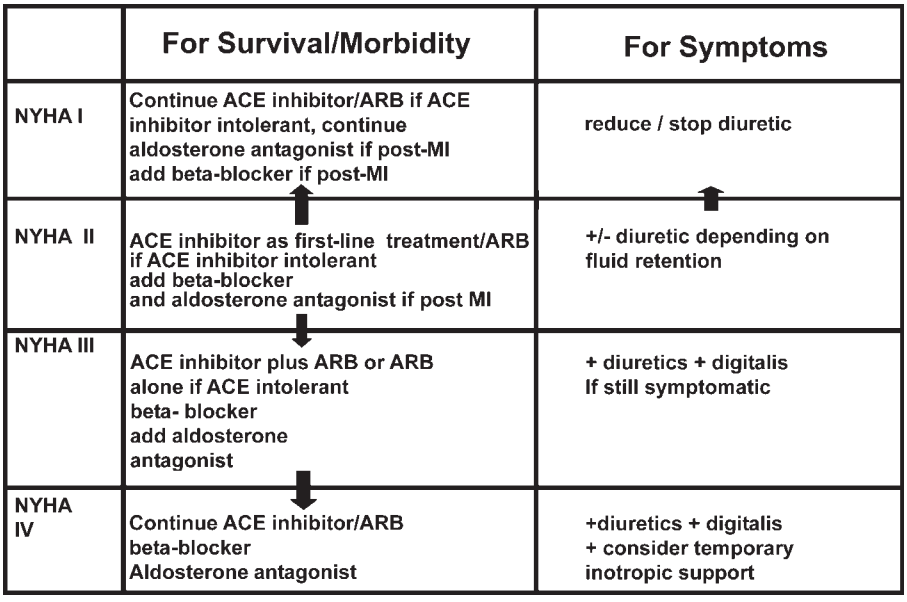

Figure 4 Pharmacological therapy of symptomatic CHF that is equally systolic left ventricular dysfunction. The algorithm should primarily be viewed as an example of how decisions on therapy can be made depending on the progression of heart failure severity. A patient in NYHA Class II can be followed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

treatments outlined in 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.

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 with preserved left ventricular ejection fraction

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

Table 19 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)
- Infection
- 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)

prevalence of diastolic dysfunction in patients with heart failure symptoms and a normal systolic function in the community. There is still little evidence from clinical trials or observational studies on how to treat heart failure with PLVEF.

Heart failure with PLVEF and heart failure due to diastolic dysfunction are not synonymous. The former diagnosis implies the evidence of preserved LVEF and not that left ventricular diastolic dysfunction has been demonstrated.

The diagnosis of isolated diastolic heart failure requires evidence of abnormal diastolic function, which may be difficult to assess. 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.[106]

Pharmacological therapy of heart failure with PLVEF or diastolic dysfunction

The following recommendations are largely speculative because of the limited data available in patients with PLVEF or diastolic dysfunction (in general, Class of recommendation IIa, level of evidence C).

There is no clear evidence that patients with primary diastolic heart failure benefit from any specific drug regimen.

(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 filling period.
(4) Verapamil-type calcium antagonists may be used for the same reason.[107] Some studies with verapamil have shown a functional improvement in patients with hypertrophic cardiomyopathy.[108]
(5) A high dose of an ARB may reduce hospitalizations.[109]

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 in general have been excluded from randomized trials. Relief of symptoms rather than prolongation of life may be the most important goal of treatment for many older patients.

ACE-inhibitors and ARBs

ACE-inhibitors and ARBs are effective and well-tolerated in elderly patients in general.

Diuretic therapy

In the elderly, thiazides are often ineffective because of reduced glomerular filtration rate. 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 sick sinus node, AV-block and obstructive lung disease are excluded. Beta-blockade should not be withheld because of increasing age alone.

Cardiac glycosides

Elderly patients may be more susceptible to adverse effects of digoxin. 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.

Arrhythmias

- It is essential to recognize and correct precipitating factors for arrhythmias, improve cardiac function and reduce neuro-endocrine activation with beta-blockade, ACE inhibition, and possibly, aldosterone receptor antagonists (Class of recommendation I, level of evidence C).

Ventricular arrhythmias

- In patients with ventricular arrhythmias, the use of anti-arrhythmic agents is only justified in patients with severe, symptomatic, sustained ventricular tachycardias and where amiodarone should be the preferred agent (Class of recommendation IIa, level of evidence B).[87,89]
- ICD implantation is indicated in patients with heart failure and with 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).[95,96,110–112]

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).[113]
- 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 depending on previous heart failure or not. Treatment strategy is depending on symptoms and haemodynamic stability. For options see.[106]

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

Table 20 Recommended components of care and following programmes (class 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 counselling
- Inpatient and outpatient (home-based)
- Attention to behavioural strategies
- Address barriers to compliance
- Early attention to signs and symptoms (e.g. telemonitoring)
- Flexible diuretic regimen

(1) optimize existing therapy, e.g. beta-blockade
(2) add long-acting nitrates
(3) if not successful, add amlodipine or felodipine
(4) consider coronary revascularization.

If hypertension is present

- optimize the dose of ACE-inhibitors, beta-blocking agents, and diuretics.[40]
- add spironolactone or ARBs if not present already
- if not successful, try second generation dihydropyridine derivatives.

Care and follow-up

See also *Table 20*.

- 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.[71,114–118]
- 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 (Class of recommendation I, level of evidence C).[119–122]

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