European Heart Journal (2008) **29**, 2388–2442
doi:10.1093/eurheartj/ehn309

ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008‡

The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM)

Authors/Task Force Members: Kenneth Dickstein (Chairperson) (Norway)*, Alain Cohen-Solal (France), Gerasimos Filippatos (Greece), John J.V. McMurray (UK), Piotr Ponikowski (Poland), Philip Alexander Poole-Wilson (UK), Anna Strömberg (Sweden), Dirk J. van Veldhuisen (The Netherlands), Dan Atar (Norway), Arno W. Hoes (The Netherlands), Andre Keren (Israel), Alexandre Mebazaa (France), Markku Nieminen (Finland), Silvia Giuliana Priori (Italy), Karl Swedberg (Sweden)

ESC Committee for Practice Guidelines (CPG): Alec Vahanian (Chairperson) (France), John Camm (UK), Raffaele De Caterina (Italy), Veronica Dean (France), Kenneth Dickstein (Norway), Gerasimos Filippatos (Greece), Christian Funck-Brentano (France), Irene Hellemans (The Netherlands), Steen Dalby Kristensen (Denmark), Keith McGregor (France), Udo Sechtem (Germany), Sigmund Silber (Germany), Michal Tendera (Poland), Petr Widimsky (Czech Republic), Jose Luis Zamorano (Spain)

Document Reviewers: Michal Tendera (CPG Review Coordinator) (Poland), Angelo Auricchio (Switzerland), Jeroen Bax (The Netherlands), Michael Böhm (Germany), Ugo Corrà (Italy), Paolo della Bella (Italy), Perry M. Elliott (UK), Ferenc Follath (Switzerland), Mihai Gheorghiade (USA), Yonathan Hasin (Israel), Anders Hernborg (Sweden), Tiny Jaarsma (The Netherlands), Michel Komajda (France), Ran Kornowski (Israel), Massimo Piepoli (Italy), Bernard Prendergast (UK), Luigi Tavazzi (Italy), Jean-Luc Vachiery (Belgium), Freek W. A. Verheugt (The Netherlands), Jose Luis Zamorano (Spain), Faiez Zannad (France)

‡Important note: The originally published version contained errors in Table 22 on p. 2412 and Table 28 on p. 2427. This version has been corrected and the errors are identified in red.

Table of contents

* Corresponding author. Chairperson: Kenneth Dickstein, University of Bergen, Cardiology Division, Stavanger University Hospital, N-4011 Stavanger, Norway. Tel: +47 51519453, Fax: +47 51 519921. Email: kenneth.dickstein@med.uib.no

These guidelines were first published on the European Society of Cardiology Web Site on 30 August 2008. This article has been copublished in the *European Journal of Heart Failure*, doi:10.1016/j.ejheart.2008.08.005.

Preamble

Guidelines and Expert Consensus Documents summarize and evaluate all currently available evidence on a particular issue with the aim of assisting physicians and other healthcare providers in selecting the best management strategies for a typical patient, suffering from a given condition, taking into account the impact on outcome, as well as the risk–benefit ratio of particular diagnostic or therapeutic means. Guidelines are no substitutes for textbooks. The legal implications of medical guidelines have been discussed previously.

A great number of Guidelines and Expert Consensus Documents have been issued in recent years by the European Society of Cardiology (ESC) as well as by other societies and organizations. Because of the impact on clinical practice, quality criteria for development of guidelines have been established in order to make all decisions transparent to the user. The recommendations for formulating and issuing ESC Guidelines and Expert Consensus Documents can be found on the ESC Web Site in the guidelines section (www.escardio.org).

In brief, experts in the field are selected and undertake a comprehensive review of the published evidence for management and/or prevention of a given condition. A critical evaluation of diagnostic and therapeutic procedures is performed, including assessment of the risk–benefit ratio. Estimates of expected health outcomes for larger societies are included, where data exist. The level of evidence and the strength of recommendation of particular treatment options are weighed and graded according to pre-defined scales, as outlined in *Tables 1* and *2*.

The experts of the writing panels have provided disclosure statements of all relationships they may have which might be perceived as real or potential sources of conflicts of interest. These

Table 1 Classes of recommendations

Classes of Recommendations	Definition
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.
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 given treatment or procedure is not useful/effective, and in some cases may be harmful.

Table 2 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, retrospective studies, registries.

disclosure forms are kept on file at the European Heart House, headquarters of the ESC. Any changes in conflict of interest that arise during the writing period must be notified to the ESC. The Task Force report was entirely supported financially by the ESC and was developed without any involvement of the industry.

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 Committee is also responsible for the endorsement process of these Guidelines and Expert Consensus Documents or statements. Once the document has been finalized and approved by all the experts involved in the Task Force, it is submitted to outside specialists for review. The document is revised, and finally approved by the CPG and subsequently published.

After publication, dissemination of the message is of paramount importance. Pocket-sized versions and personal digital assistant (PDA)-downloadable versions are useful at the point of care. Some surveys have shown that the intended end-users are sometimes not aware of the existence of guidelines, or simply do not translate them into practice, so this is why implementation programmes for new guidelines form an important component of the dissemination of knowledge. Meetings are organized by the ESC, and directed towards its member National Societies and key opinion leaders in Europe. Implementation meetings can also be undertaken at national levels, once the guidelines have been endorsed by the ESC member societies, and translated into the national language. Implementation programmes are needed because it has been shown that the outcome of disease may be favourably influenced by the thorough application of clinical recommendations.

Thus, the task of writing Guidelines or Expert Consensus documents covers not only the integration of the most recent research, but also the creation of educational tools and implementation programmes for the recommendations. The loop between clinical research, writing of guidelines, and implementing them into clinical practice can then only be completed if surveys and registries are performed to verify that real-life daily practice is in keeping with what is recommended in the guidelines. Such surveys and registries also make it possible to evaluate the impact of implementation of the guidelines on patient outcomes. Guidelines and recommendations should help physicians and other healthcare providers to make decisions in their daily practice. However, the ultimate judgement regarding the care of an individual patient must be made by the physician in charge of his/her care.

Introduction

Heart failure guidelines

The aim of this document is to provide practical guidelines for the diagnosis, assessment, and treatment of acute and chronic heart failure (HF). These guidelines are a development and revision of guidelines published in 1995,[1] 1997,[2] 2001,[3] and 2005.[4,5] Much new information relating to the treatment of HF has emerged. This has necessitated a revision of some previous recommendations. The recommendations are relevant to clinical practice, epidemiological surveys, observational studies, and clinical trials. Particular attention in this revision has been given to the simplification and clarity of recommendations, and to the problems associated with implementation. The intention has been to merge and modify previous documents relating to HF. The guidelines are intended as a support for practising physicians and other healthcare professionals providing advice on how to manage these patients, including recommendations for referral. Documented and published evidence on diagnosis, efficacy, and safety of therapeutic interventions is the main basis for these guidelines. Where evidence is lacking or does not resolve a clinical issue, a consensus opinion is presented.

ESC Guidelines are relevant to 51 member states with diverse economies and, therefore, recommendations based on cost-effectiveness have, in general, been avoided. National health policy as well as clinical judgement may dictate the order of priorities in implementation. The recommendations in these guidelines should always be considered in the light of national policies and local regulatory guidance on the use 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 CPG and the document reviewers (see title page). After consideration of their input, the document was updated, reviewed, and then approved for publication by the entire Task Force. An evidence-based approach has been used to generate the grade of any recommendation in the guidelines, with an additional assessment of the quality of the evidence. For the diagnosis of HF, evidence is incomplete. Where that is so, recommendations and statements are based on a consensus of expert opinions.

Definition and diagnosis

Definition of heart failure

Many definitions of HF have been put forward over the last 50 years.[6] These highlight one or several features of this complex syndrome such as haemodynamics, oxygen consumption, or exercise capacity. In recent years, most definitions have emphasized the need for both the presence of symptoms of HF and physical signs of fluid retention.[5,7–9]

HF is a syndrome in which the patients should have the following features: symptoms of HF, typically shortness of breath at rest or during exertion, and/or fatigue; signs of fluid retention such as pulmonary congestion or ankle swelling; and objective evidence of an abnormality of the structure or function of the heart at rest (*Table 3*). A clinical response to treatment directed at HF alone is not sufficient for the diagnosis, but is helpful when the diagnosis remains unclear after appropriate diagnostic investigations. Patients with HF would usually be expected to show some improvement in symptoms and signs in response to those treatments from which a relatively fast symptomatic improvement could be anticipated (e.g. diuretic or vasodilator administration). The major and common clinical manifestations of HF are shown in *Table 4*.

Asymptomatic structural or functional abnormalities of the heart are considered as precursors of symptomatic HF and are associated with a high mortality.[10,11] Treatment is available for these

conditions, when diagnosed, and for that reason these conditions are included in these guidelines.

An advantage of the definition of HF used here is that it is practical and allows a more precise approach both in clinical practice and when undertaking observational surveys, epidemiological studies, or clinical trials. HF should never be a sole diagnosis. The cause should always be sought.

Descriptive terms in heart failure

Acute and chronic heart failure

Many additional words or phrases are used to characterize patients with HF. These terms can overlap, and physicians do sometimes use words with a slightly different meaning. The word 'acute' in the context of acute HF has become confusing because some clinicians use the word to indicate severity (the medical emergency of life-threatening pulmonary oedema) and others use the word to indicate decompensated, recent-onset, or even new-onset HF.[4] The word is then an indicator of time rather than severity. The words acute, advanced, and decompensated should not be used interchangeably when applied to HF. A useful classification of HF based on the nature of the clinical presentation is shown in *Table 5*. A distinction is made between new-onset HF, transient HF, and chronic HF. New-onset HF is self-explanatory and refers to the first presentation. Transient HF refers to symptomatic HF over a limited time period, although long-term treatment may be indicated. Examples would be patients with mild myocarditis from which recovery is near complete, patients with a myocardial infarction (MI) who need diuretics in the coronary care unit but in whom long-term treatment is not necessary, or transient HF caused by ischaemia and resolved by revascularization. Worsening HF on a background of chronic HF (decompensation) is by far the most common form of HF leading to hospital admission, accounting for 80% of cases. Treatment should be based on the clinical presentation for which specific therapy is indicated (e.g. pulmonary oedema, hypertension emergency, acute MI).

Table 3 Definition of heart failure

Heart failure is a clinical syndrome in which patients have the following features:

- **Symptoms typical of heart failure**
  (breathlessness at rest or on exercise, fatigue, tiredness, ankle swelling)
  and
- **Signs typical of heart failure**
  (tachycardia, tachypnoea, pulmonary rales, pleural effusion, raised jugular venous pressure, peripheral oedema, hepatomegaly)
  and
- **Objective evidence of a structural or functional abnormality of the heart at rest**
  (cardiomegaly, third heart sound, cardiac murmurs, abnormality on the echocardiogram, raised natriuretic peptide concentration)

Systolic vs. diastolic heart failure

A distinction is frequently made between systolic and diastolic HF.[12,13] The distinction is somewhat arbitrary.[14–16] Patients with diastolic HF have symptoms and/or signs of HF and a preserved left ventricular ejection fraction (LVEF) >40–50%.[17] There is no consensus concerning the cut-off for preserved EF. The EF is the stroke volume divided by the end-diastolic volume for the relevant ventricular chamber of the heart and is therefore largely determined by the end-diastolic volume of the ventricular chamber (i.e. a dilated heart). An EF below or above 40%, distinguishes between large or normal left end-diastolic ventricular volumes. The distinction has arisen largely because in the past most patients admitted to hospitals for investigation or entered into clinical trials have had dilated hearts with a reduced EF <35 or 40%. Most patients with HF have evidence of both systolic and diastolic dysfunction at rest or on exercise. Diastolic and systolic HFs should not be considered as separate entities.[18] Other phrases have been used to describe diastolic HF, such as HF with preserved ejection fraction (HFPEF), HF with normal ejection fraction (HFNEF), or HF with preserved systolic function (HFPSF). We have elected to use the abbreviation HFPEF in this document.

Table 4 Common clinical manifestations of heart failure

Dominant clinical feature	Symptoms	Signs
Peripheral oedema/congestion	Breathlessness Tiredness, fatigue Anorexia	Peripheral oedema Raised jugular venous pressure Pulmonary oedema Hepatomegaly, ascites Fluid overload (congestion) Cachexia
Pulmonary oedema	Severe breathlessness at rest	Crackles or rales over lungs, effusion Tachycardia, tachypnoea
Cardiogenic shock (low output syndromes)	Confusion Weakness Cold periphery	Poor peripheral perfusion SBP <90 mmHg Anuria or oliguria
High blood pressure (hypertensive heart failure)	Breathlessness	Usually raised BP, LV hypertrophy, and preserved EF
Right heart failure	Breathlessness Fatigue	Evidence of RV dysfunction Raised JVP, peripheral oedema, hepatomegaly, gut congestion

Other descriptive terms in heart failure

Many other phrases have been used in describing patients with HF that do not have aetiological significance. Forward and backward HF are old terms used to express the concept that perfusion of tissue and an increase in the left atrial pressure can under some circumstance such as acute HF and cardiogenic shock contribute to the pathophysiology.[19,20] Preload and afterload are terms linked to the left and/or right atrial pressures (often reflecting volume overload) and the work of the myocardium (often reflecting pressure overload or high impedance). However, measures of these parameters are often imprecise. Right and left HF refer to syndromes presenting predominantly with congestion of the systemic or pulmonary veins, leading to signs of fluid retention with ankle swelling or pulmonary oedema, respectively. The most common cause of right ventricular failure is a raised pulmonary artery pressure due to failure of the LV leading to poor perfusion of the kidney, retention of salt and water, and accumulation of fluid in the systemic circulation. High and low output HF refer to the observation that a number of specific medical conditions lead to a clinical picture which mimics the signs and symptoms of HF. Common causes of high output states mimicking HF are anaemia, thyrotoxicosis, septicaemia, liver failure, arteriovenous shunts, Paget's disease, and beri-beri. In these conditions, the primary abnormality is not disease of the heart and the conditions are reversible with treatment. The conditions are better labelled as HF secondary to circulatory high output conditions and are important because they are treatable and should be excluded when diagnosing HF.

Table 5 Classification of heart failure

• **New onset**	First presentation Acute or slow onset
• **Transient**	Recurrent or episodic
• **Chronic**	Persistent Stable, worsening, or decompensated

Mild, moderate, or severe HF 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. Two classifications (*Table 6*) of the severity of HF are commonly employed. One is based on symptoms and exercise capacity [the New York Heart Association (NYHA) functional classification[21,22]]. The NYHA functional classification has proved to be clinically useful and it is employed routinely in most randomized clinical trials. The other describes HF in stages based on structural changes and symptoms. All patients with overt HF are in stages C and D.[7]

Epidemiology

Much is now known about the epidemiology of HF.[23–27] The ESC represents countries with a population of >900 million, and there are at least 15 million patients with HF in those 51 countries. The prevalence of asymptomatic ventricular dysfunction is similar, so that HF or asymptomatic ventricular dysfunction is evident in ~4% of the population. The prevalence of HF is between 2 and 3% and rises sharply at ~75 years of age, so the prevalence in 70- to 80-year-old people is between 10 and 20%. In younger age groups HF is more common in men because the most common cause, coronary heart disease, occurs in earlier decades. In the elderly, the prevalence is equal between the sexes.

The overall prevalence of HF is increasing because of the ageing of the population, the success in prolonging survival in patients suffering coronary events, and the success in postponing coronary events by effective prevention in those at high risk or those who have already

Table 6 Classification of heart failure by structural abnormality (ACC/AHA), or by symptoms relating to functional capacity (NYHA)

ACC/AHA stages of heart failure		NYHA functional classification	
Stage of heart failure based on structure and damage to heart muscle		**Severity based on symptoms and physical activity**	
Stage A	At high risk for developing heart failure. No identified structural or functional abnormality; no signs or symptoms.	**Class I**	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnoea.
Stage B	Developed structural heart disease that is strongly associated with the development of heart failure, but without signs or symptoms.	**Class II**	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnoea.
Stage C	Symptomatic heart failure associated with underlying structural heart disease.	**Class III**	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity results in fatigue, palpitation, or dyspnoea.
Stage D	Advanced structural heart disease and marked symptoms of heart failure at rest despite maximal medical therapy.	**Class IV**	Unable to carry on any physical activity without discomfort. Symptoms at rest. If any physical activity is undertaken, discomfort is increased.

ACC = American College of Cardiology; AHA = American Heart Association. Hunt SA *et al. Circulation* 2005;**112**:1825–1852.
The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Little Brown & Co; 1994. pp 253–256.

survived a first event (secondary prevention).[28,29] In some countries the age-adjusted mortality from HF is falling at least in part due to modern treatment.[28,30–32] The mean age of patients with HF in the community in developed countries is 75 years. HFPEF is more common in the elderly, women, and those with hypertension or diabetes. HF is the cause of 5% of acute hospital admissions, is present in 10% of patients in hospital beds, and accounts for ~2% of national expenditure on health, mostly due to the cost of hospital admissions.[33] Substantial under-reporting is probably due to clinicians' preference for aetiological diagnoses (e.g. aortic stenosis) or the diagnosis of a major co-morbidity (e.g. diabetes).

The outlook is, in general, gloomy, although some patients can live for many years.[23,29,34,35] Overall 50% of patients are dead at 4 years. Forty per cent of patients admitted to hospital with HF are dead or readmitted within 1 year.

Studies show that the accuracy of diagnosis of HF by clinical means alone is often inadequate, particularly in women, the elderly, and the obese.[36,37] HFPEF (EF >45–50%) is present in half the patients with HF. The prognosis in more recent studies has been shown to be essentially similar to that of systolic HF.[38,39]

Aetiology of heart failure

There are only a limited number of ways in which the function of the heart can be affected. The most common causes of functional deterioration of the heart are damage or loss of heart muscle, acute or chronic ischaemia, increased vascular resistance with hypertension, or the development of a tachyarrhythmia such as atrial fibrillation (AF). Coronary heart disease is by far the most common cause of myocardial disease, being the initiating cause in ~70% of patients with HF.[28,40] Valve disease accounts for 10% and cardiomyopathies for another 10% (*Table 7*).

A cardiomyopathy is a myocardial disorder in which the heart muscle is structurally and functionally abnormal [in the absence of coronary artery disease (CAD), hypertension, valvular disease, or congenital heart disease] sufficient to cause the observed myocardial abnormality.[41]

A classification of the cardiomyopathies has been published recently by the Working Group on Myocardial and Pericardial Diseases of the ESC.[41] The American Heart Association has issued a scientific statement.[42] Both take into account the great advances made recently in understanding the genetic origins and the biology of the cardiomyopathies. The European proposal was guided by the relevance of the new classification to everyday clinical practice and maintains the previously defined morpho-functional phenotypes which are further subdivided into familial/genetic and non-familial/non-genetic forms. The European classification abandoned the older distinction between 'primary' and 'secondary' cardiomyopathies, and does not include ion channelopathies among cardiomyopathies.

Table 7 Common causes of heart failure due to disease of heart muscle (myocardial disease)

Coronary heart disease	Many manifestations
Hypertension	Often associated with left ventricular hypertrophy and preserved ejection fraction
Cardiomyopathies*	Familial/genetic or non-familial/non-genetic (including acquired, e.g. myocarditis)
	Hypertrophic (HCM), dilated (DCM), restrictive (RCM), arrhythmogenic right ventricular (ARVC), unclassified
Drugs	β-Blockers, calcium antagonists, antiarrhythmics, cytotoxic agents
Toxins	Alcohol, medication, cocaine, trace elements (mercury, cobalt, arsenic)
Endocrine	Diabetes mellitus, hypo/hyperthyroidism, Cushing syndrome, adrenal insufficiency, excessive growth hormone, phaeochromocytoma
Nutritional	Deficiency of thiamine, selenium, carnitine. Obesity, cachexia
Infiltrative	Sarcoidosis, amyloidosis, haemochromatosis, connective tissue disease
Others	Chagas' disease, HIV infection, peripartum cardiomyopathy, end-stage renal failure

*See text for details.

Table 8 Key features of the clinical history in patients with heart failure

Symptoms	Breathlessness	(orthopnoea, paroxysmal nocturnal dyspnoea)
	Fatigue	(tiredness, exhaustion)
	Angina, palpitations, syncope	
Cardiovascular events	Coronary heart disease	
	Myocardial infarction	Thrombolysis
	Intervention	PCI
	Other surgery	CABG
	Stroke or peripheral vascular disease	
	Valvular disease or dysfunction	
Risk profile	Family history, smoking, hyperlipidaemia, hypertension, diabetes	
Response to current and previous therapy		

Diagnosis of heart failure

In 1933 Sir Thomas Lewis wrote in his textbook on heart disease that 'The very essence of cardiovascular medicine is the recognition of early heart failure'.[43]

Symptoms and signs of heart failure

The symptoms and signs of HF are the key to early detection because that is what causes patients to seek medical attention.Taking a good history and careful physical examination are skills, which are essential to master (*Table 8*). Breathlessness, tiredness, and fatigue are the characteristic symptoms, but eliciting and assessing these symptoms particularly in the elderly requires experience and skill.[44–46] The clinical signs of HF (*Table 9*) should be assessed in a careful clinical examination, including observation, palpation, and auscultation.[47–51] Like symptoms, the signs of early HF can be difficult to interpret, not only in elderly patients, but also in the obese. The clinical suspicion of HF must then be confirmed by more objective tests particularly targeting assessment of cardiac function.

The causes of symptoms in heart failure

The origins of the symptoms of HF are not fully understood.[52–55] Increased pulmonary capillary pressure is undoubtedly responsible for pulmonary oedema and shortness of breath in the context of acute HF with evidence of fluid overload. In contrast, studies conducted during exercise in patients with chronic HF demonstrate only a weak relationship between capillary pressure and exercise performance. HF is a condition which eventually results in pathology in almost all body organs. Tiredness and fatigue are frequently reported symptoms, but are non-specific with multiple causes. Loss of skeletal muscle mass and strength is a late manifestation.[55,56] Signals from skeletal muscle are often interpreted by the brain as breathlessness or as fatigue. This may explain why the response to treatment may be slow in patients with HF because the quality of skeletal muscle must be restored. Variation in the degree of mitral regurgitation or transitory dysrhythmia, common in HF, will also exacerbate breathlessness.

Table 9 Key features of the clinical examination in patients with heart failure

Appearance	Alertness, nutritional status, weight
Pulse	Rate, rhythm, and character
Blood pressure	Systolic, diastolic, pulse pressure
Fluid overload	Jugular venous pressure Peripheral oedema (ankles and sacrum) hepatomegaly, ascites
Lungs	Respiratory rate Rales Pleural effusion
Heart	Apex displacement Gallop rhythm, third heart sound Murmurs suggesting valvular dysfunction

Symptoms and severity of heart failure

There is a poor relationship between symptoms and the severity of cardiac dysfunction. Symptoms do relate more closely to prognosis if persistent after therapy and can then be used to classify the severity of HF and to monitor the effects of therapy. However, symptoms alone should not guide the optimal titration of neurohormonal inhibitors such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), β-blockers, or aldosterone antagonists, because these drugs impact on mortality in a manner that is not closely related to symptoms. Patients should be titrated to the optimal, tolerated dose.

The severity of heart failure is most often classified using the NYHA functional classification. A more recent classification is based on both the structure of the heart and symptoms. In the context of MI, two other classifications of the severity of HF, the Killip[57] and Forrester[58] classifications, are used (*Table 10*).

Algorithm for the diagnosis of heart failure

An algorithm for the diagnosis of HF or LV dysfunction is shown in *Figure 1*. The diagnosis of HF is not sufficient alone. Appropriate investigations are required to establish the cause of the HF, because although the general treatment of HF is common to

Table 10 Two classifications of the severity of heart failure in the context of acute myocardial infarction

Killip classification		Forrester classification
Designed to provide a clinical estimate of the severity of circulatory derangement in the treatment of acute myocardial infarction.		Designed to describe clinical and haemodynamic status in acute myocardial infarction.
Stage I	No heart failure. No clinical signs of cardiac decompensation	1. Normal perfusion and pulmonary wedge pressure (PCWP—estimate of left atrial pressure)
Stage II	Heart failure. Diagnostic criteria include rales, S3 gallop, and pulmonary venous hypertension. Pulmonary congestion with wet rales in the lower half of the lung fields.	2. Poor perfusion and low PCWP (hypovolaemic) 3. Near normal perfusion and high PCWP (pulmonary oedema)
Stage III	Severe heart failure. Frank pulmonary oedema with rales throughout the lung fields	4. Poor perfusion and high PCWP (cardiogenic shock)
Stage IV	Cardiogenic shock. Signs include hypotension (SBP <90 mmHg), and evidence of peripheral vasoconstriction such as oliguria, cyanosis and sweating	

Killip T, 3rd, Kimball JT. Treatment of myocardial infarction in a coronary care unit. A two year experience with 250 patients. *Am J Cardiol* 1967;**20**:457–464.
Forrester JS, Diamond GA, Swan HJ. Correlative classification of clinical and hemodynamic function after acute myocardial infarction. *Am J Cardiol* 1977;**39**:137–145.

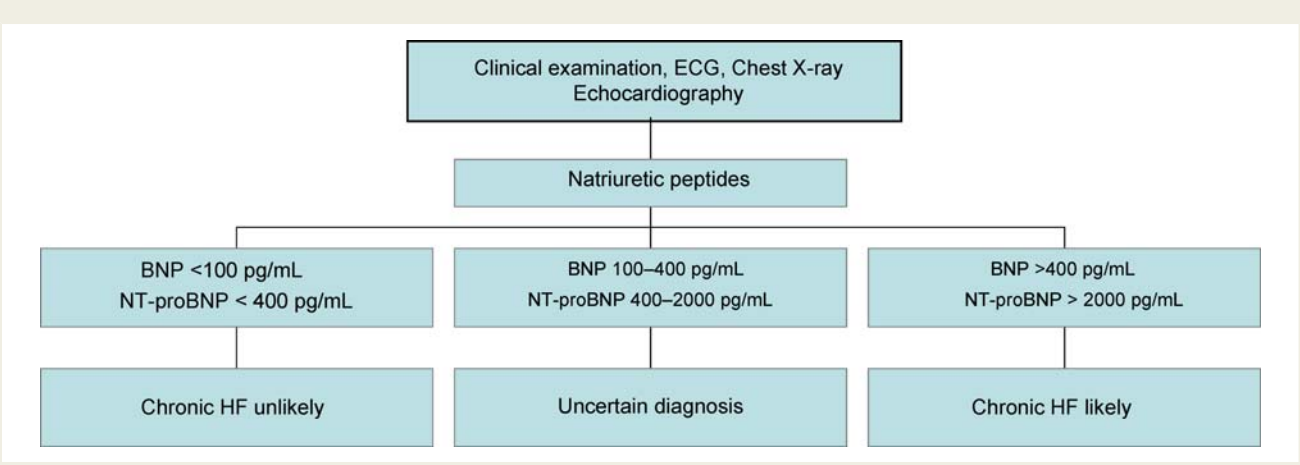

Figure 1 Flow chart for the diagnosis of HF with natriuretic peptides in untreated patients with symptoms suggestive of HF.

most patients, some causes require specific treatments and may be correctable.

Diagnostic techniques

Diagnostic tests in heart failure

Several diagnostic tests are employed routinely to confirm or rule out the diagnosis of HF (*Table 11*). Diagnostic tests are usually most sensitive for the detection of patients with HF and reduced EF. Diagnostic findings are often less pronounced in patients with HFPEF. Echocardiography is the most useful method for evaluating systolic and diastolic dysfunction.

The following investigations are considered appropriate in patients with HF. However, the recommendations largely represent expert consensus opinion without adequate documented evidence. Level of evidence C applies unless otherwise stated.

Electrocardiogram

An electrocardiogram (ECG) should be performed in every patient with suspected heart failure.

Electrocardiographic changes are common in patients suspected of having HF (*Table 12*). An abnormal ECG has little predictive value for the presence of HF. If the ECG is completely normal, HF, especially with systolic dysfunction, is unlikely (<10%).

Chest X-ray

Chest X-ray is an essential component of the diagnostic work-up in heart failure. It permits assessment of pulmonary congestion and may demonstrate important pulmonary or thoracic causes of dyspnoea.

The chest X-ray (in two planes) is useful to detect cardiomegaly, pulmonary congestion, and pleural fluid accumulation, and can demonstrate the presence of pulmonary disease or infection causing or contributing to dyspnoea (*Table 13*). Apart from congestion, findings are predictive of HF only in the context of typical signs and symptoms. Cardiomegaly can be absent not only in acute but also in chronic HF.

Table 11 Diagnostic assessments supporting the presence of heart failure

Assessment	Diagnosis of heart failure	
	Supports if present	Opposes if normal or absent
Compatible symptoms	++	++
Compatible signs	++	+
Cardiac dysfunction on echocardiography	+++	+++
Response of symptoms or signs to therapy	+++	++
ECG		
Normal		++
Abnormal	++	+
Dysrhythmia	+++	+
Laboratory		
Elevated BNP/NT-proBNP	+++	+
Low/normal BNP/NT-proBNP	+	+++
Hyponatraemia	+	+
Renal dysfunction	+	+
Mild elevations of troponin	+	+
Chest X-ray		
Pulmonary congestion	+++	+
Reduced exercise capacity	+++	++
Abnormal pulmonary function tests	+	+
Abnormal haemodynamics at rest	+++	++

+ = some importance; ++ = intermediate importance; +++ = great importance.

Laboratory tests

A routine diagnostic evaluation of patients with suspected HF includes a complete blood count (haemoglobin, leukocytes, and

Table 12 Common ECG abnormalities in heart failure

Abnormality	Causes	Clinical implications
Sinus tachycardia	Decompensated HF, anaemia, fever, hyperthyroidism	Clinical assessment Laboratory investigation
Sinus bradycardia	β-Blockade, digoxin Anti-arrhythmics Hypothyroidism Sick sinus syndrome	Evaluate drug therapy Laboratory investigation
Atrial tachycardia/flutter/ fibrillation	Hyperthyroidism, infection, mitral valve diseases Decompensated HF, infarction	Slow AV conduction, medical conversion, electroversion, catheter ablation, anticoagulation
Ventricular arrhythmias	Ischemia, infarction, cardiomyopathy, myocarditis hypokalaemia, hypomagnesaemia Digitalis overdose	Laboratory investigation Exercise test, perfusion studies, coronary angiography, electrophysiology testing, ICD
Ischaemia/Infarction	Coronary artery disease	Echo, troponins, coronary angiography, revascularization
Q waves	Infarction, hypertrophic cardiomyopathy LBBB, pre-excitation	Echo, coronary angiography
LV hypertrophy	Hypertension, aortic valve disease, hypertrophic cardiomyopathy	Echo/Doppler
AV block	Infarction, drug toxicity, myocarditis, sarcoidosis, Lyme disease	Evaluate drug therapy, pacemaker, systemic disease
Microvoltage	Obesity, emphysema, pericardial effusion, amyloidosis	Echo, chest X-ray
QRS length >120 ms of LBBB morphology	Electrical and mechanical dysynchrony	Echo CRT-P, CRT-D

Table 13 Common chest X-ray abnormalities in heart failure

Abnormality	Causes	Clinical Implications
Cardiomegaly	Dilated LV, RV, atria Pericardial effusion	Echo/Doppler
Ventricular hypertrophy	Hypertension, aortic stenosis, hypertrophic cardiomyopathy	Echo/Doppler
Normal pulmonary findings	Pulmonary congestion unlikely	Reconsider diagnosis (if untreated) Serious lung disease unlikely
Pulmonary venous congestion	Elevated LV filling pressure	Left heart failure confirmed
Interstitial oedema	Elevated LV filling pressure	Left heart failure confirmed
Pleural effusions	Elevated filling pressures HF likely if bilateral Pulmonary infection, surgery, or malignant effusion	Consider non-cardiac aetiology if abundant If abundant, consider diagnostic or therapeutic centres
Kerley B lines	Increased lymphatic pressures	Mitral stenosis or chronic HF
Hyperlucent lung fields	Emphysema or pulmonary embolism	Spiral CT, spirometry, Echo
Pulmonary infection	Pneumonia may be secondary to pulmonary congestion	Treat both infection and HF
Pulmonary infiltration	Systemic disease	Diagnostic work-up

platelets), serum electrolytes, serum creatinine, estimated glomerular filtration rate (GFR), glucose, liver function tests, and urinalysis. Additional tests should be considered according to the clinical picture (*Table 14*). Marked haematological or electrolyte abnormalities are uncommon in untreated mild to moderate HF, although mild anaemia, hyponatraemia, hyperkalaemia, and reduced renal function are common, especially in patients treated with diuretics and ACEI/ARB/aldosterone antagonist therapy. Appropriate laboratory monitoring is essential during the initiation, titration, and follow-up phases in patients receiving drug therapy for HF.

Natriuretic peptides

Plasma concentrations of natriuretic peptides are useful biomarkers in the diagnosis of HF and in the management of patients with established chronic HF. Evidence exists supporting their use for diagnosing, staging, making hospitalization/discharge decisions, and identifying patients at risk for clinical events. The evidence for their use in monitoring and adjusting drug therapy is less clearly established. A normal concentration in an untreated patient has a high negative predictive value and makes HF an unlikely cause of symptoms. This may play an important role especially

Table 14 Common laboratory test abnormalities in heart failure

Abnormality	Cause	Clinical implications
Increased serum creatinine (>150 μmol/L)	Renal disease ACEI/ARB, aldosterone blockade	Calculate GFR, Consider reducing ACEI/ARB, or aldosterone blocker dose Check potassium and BUN
Anaemia (<13 g/dL in men, <12 in women)	Chronic HF, haemodilution, iron loss or poor utilization, renal failure, chronic disease	Diagnostic work-up Consider treatment
Hyponatraemia (<135 mmol/L)	Chronic HF, haemodilution. AVP release, diuretics	Consider water restriction, reducing diuretic dosage Ultrafiltration, vasopressin antagonist
Hypernatraemia (>150 mmol/L)	Hyperglycaemia Dehydratation	Assess water intake Diagnostic work-up
Hypokalaemia (<3.5 mmol/L)	Diuretics, secondary hyperaldosteronism	Risk of arrhythmia Consider potassium supplements, ACEIs/ARB, aldosterone blockers
Hyperkalaemia (>5.5 mmol/L)	Renal failure, potassium supplement, renin–angiotensin–aldosterone system blockers	Stop potassium-sparing treatment (ACEIs/ARB, aldosterone blockers) Assess renal function and pH Risk of bradycardia
Hyperglycaemia (>6.5 mmol/L)	Diabetes, insulin resistance	Evaluate hydration, treat glucose intolerance
Hyperuricaemia (>500 μmol/L)	Diuretic treatment, gout, malignancy	Allopurinol Reduce diuretic dose
BNP >400 pg/mL, NT-proBNP >2000 pg/mL	Increased ventricular wall stress	HF likely Indication for echo Consider treatment
BNP <100 pg/mL, NT-proBNP <400 pg/mL	Normal wall stress	Re-evaluate diagnosis HF unlikely if untreated
Albumin high (>45 g/L)	Dehydratation, myeloma	Rehydrate
Albumin low (<30 g/L)	Poor nutrition, renal loss	Diagnostic work-up
Transaminase increase	Liver dysfunction Right heart failure Drug toxicity	Diagnostic work-up Liver congestion Reconsider therapy
Elevated troponins	Myocyte necrosis Prolonged ischaemia, severe HF, myocarditis, sepsis, renal failure, pulmonary embolism	Evaluate pattern of increase (mild increases common in severe HF) Coronary angiography Evaluation for revascularization
Abnormal thyroid tests	Hyper/hypothyroidism Amiodarone	Treat thyroid abnormality
Urinalysis	Proteinuria, glycosuria, bacteria	Diagnostic work-up Rule out infection
INR >2.5	Anticogulant overdose Liver congestion	Evaluate anticoagulant dosage Assess liver function Assess anticoagulant dose
CRP >10 mg/L, neutrophilic leukocytosis	Infection, inflammation	Diagnostic work-up

in primary care. High levels of natriuretic peptides despite optimal treatment indicate a poor prognosis.

B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) measurements were introduced as tools for diagnosis[59] and management[60] of HF (*Figure 1*). They rise in response to an increase in myocardial wall stress. Usually, lower levels are observed in patients with preserved LV systolic function. There is no definitive cut-off value recognized for either of the two natriuretic peptides commonly assessed for the diagnosis of HF in the emergency department. Due to the relatively long half-lives of natriuretic peptides, abrupt changes in LV filling pressures may not be reflected by rapid changes in peptides. Conditions other than HF associated with elevated natriuretic peptide levels include: LV hypertrophy, tachycardia, right ventricular overload, myocardial ischaemia, hypoxaemia, renal dysfunction, advanced age, liver cirrhosis, sepsis, and infection. Obesity and treatment may decrease natriuretic peptide levels. Natriuretic peptides may also be useful in assessing prognosis prior to hospital discharge and in monitoring the effectiveness of HF therapy.[61,62]

Troponins

Troponin I or T should be sampled in suspected HF when the clinical picture suggests an acute coronary syndrome (ACS). An increase in cardiac troponins indicates myocyte necrosis and, if indicated, the potential for revascularization should be considered and an appropriate diagnostic work-up performed. An increase in troponin also occurs in acute myocarditis. Mild increases in cardiac troponins are frequently seen in severe HF or during episodes of HF decompensation in patients without evidence of myocardial ischaemia due to ACS and in situations such as sepsis. An elevated troponin is a strong prognostic marker in HF, especially in the presence of elevated natriuretic peptides.[63]

Neurohormonal markers

HF is accompanied by an increase in various other neurohormonal markers (norepinephrine, renin, aldosterone, endothelin, arginine vasopressin). Although useful in research, evaluation of neuroendocrine activation is not required for diagnostic or prognostic purposes in individual patients.

Echocardiography

The term echocardiography is used to refer to all cardiac ultrasound imaging techniques, including pulsed and continuous wave Doppler, colour Doppler and tissue Doppler imaging (TDI).

Confirmation by echocardiography of the diagnosis of heart failure and/or cardiac dysfunction is mandatory and should be performed shortly following suspicion of the diagnosis of HF. Echocardiography is widely available, rapid, non-invasive, and safe, and provides extensive information on cardiac anatomy (volumes, geometry, mass), wall motion, and valvular function. The study provides essential information on the aetiology of HF. In general a diagnosis of heart failure should include an echocardiogram.

The most practical measurement of ventricular function for distinguishing between patients with systolic dysfunction and patients with preserved systolic function is the LVEF (normal >45–50%). This cut-off is somewhat arbitrary. LVEF is not synonymous with indices of contractility as it is strongly dependent on volumes, preload, afterload, heart rate, and valvular function. Stroke volume may be maintained by cardiac dilatation and increased volumes. *Tables 15* and *16* present the most common echocardiographic and Doppler abnormalities in HF.

Assessment of left ventricular diastolic function

Assessment of diastolic function using evaluation of the ventricular filling pattern is important for detecting abnormalities of diastolic function or filling in patients with HF. This can be the predominant functional abnormality of the heart, thus fulfilling the third component necessary for the diagnosis of heart failure. This is

Table 15 Common echocardiographic abnormalities in heart failure

Measurement	Abnormality	Clinical implications
LV ejection fraction	Reduced (<45–50%)	Systolic dysfunction
LV function, global and focal	Akinesis, hypokinesis, dyskinesis	Myocardial infarction/ischaemia Cardiomyopathy, myocarditis
End-diastolic diameter	Increased (>55–60 mm)	Volume overload HF likely
End-systolic diameter	Increased (>45 mm)	Volume overload HF likely
Fractional shortening	Reduced (<25%)	Systolic dysfunction
Left atrial size	Increased (>40 mm)	Increased filling pressures Mitral valve dysfunction Atrial fibrillation
Left ventricular thickness	Hypertrophy (>11–12 mm)	Hypertension, aortic stenosis, hypertrophic cardiomyopathy
Valvular structure and function	Valvular stenosis or regurgitation (especially aortic stenosis and mitral insufficiency)	May be primary cause of HF or complicating factor Assess gradients and regurgitant fraction Assess haemodynamic consequences Consider surgery
Mitral diastolic flow profile	Abnormalities of the early and late diastolic filling patterns	Indicates diastolic dysfunction and suggests mechanism
Tricuspid regurgitation peak velocity	Increased (>3 m/s)	Increased right ventricular systolic pressure Suspect pulmonary hypertension
Pericardium	Effusion, haemopericardium, thickening	Consider tamponade, uraemia, malignancy, systemic disease, acute or chronic pericarditis, constrictive pericarditis
Aortic outflow velocity time integral	Reduced (<15 cm)	Reduced low stroke volume
Inferior vena cava	Dilated Retrograde flow	Increased right atrial pressures Right ventricular dysfunction Hepatic congestion

Table 16 Doppler-echocardiographic indices and ventricular filling

Doppler indices	Pattern	Consequence
E/A waves ratio	Restrictive (>2, short deceleration time <115 to 150 ms)	High filling pressures Volume overload
	Slowed relaxation (<1)	Normal filling pressures Poor compliance
	Normal (>1)	Inconclusive as may be pseudo-normal
E/Ea	Increased (>15)	High filling pressures
	Reduced (<8)	Low filling pressures
	Intermediate (8–15)	Inconclusive
(A mitral–A pulm) duration	>30 ms	Normal filling pressures
	<30 ms	High filling pressures
Pulmonary S wave	>D wave	Low filling pressures
Vp	<45 cm/s	Slow relaxation
E/Vp	>2.5	High filling pressures
	<2	Low filling pressures
Valsalva manoeuvre	Change of the pseudonormal to abnormal filling pattern	Unmasks high filling pressure in the setting of systolic and diastolic dysfunction

especially true in symptomatic patients with preserved LVEF. A recent consensus paper from the Heart Failure Association has focused on the assessment of diastolic dysfunction in HFPEF.[64]

There are three types of abnormal filling patterns recognized conventionally in patients in sinus rhythm.

1. 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 may be seen at an early stage of diastolic dysfunction; it is frequently seen in hypertension and in the normal elderly subject, and is generally associated with normal or low LV filling pressures.
2. In patients with elevated left atrial pressure, (decreased LV compliance, volume overload, mitral insufficiency), 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.
3. In patients with an intermediate pattern between impaired relaxation and restrictive filling, the E/A ratio and the deceleration time may be normal, and a so-called 'pseudo-normalized filling pattern' may be seen. This pattern may be distinguished from normal filling by analysis of other Doppler variables such as pulmonary venous flow or TDI of the mitral plane motion.

Doppler echocardiography allows estimation of the systolic pulmonary artery pressure. This is derived from calculation of the right ventricular systolic pressure estimated from the peak velocity of the tricuspid regurgitant jet velocity present in most subjects. It also permits an assessment of stroke volume and cardiac output by measurement of the velocity time integral (VTI) of the aortic flow.

Assessment of heart failure with preserved ejection fraction (HFPEF)

Echocardiography plays a major role in confirming the diagnosis of HFPEF. The diagnosis of HFPEF requires three conditions to be satisfied:

1. Presence of signs and/or symptoms of chronic HF.
2. Presence of normal or only mildly abnormal LV systolic function (LVEF ≥45–50%).
3. Evidence of diastolic dysfunction (abnormal LV relaxation or diastolic stiffness).

Transoesophageal echocardiography

Transoesophageal echocardiography (TOE) is recommended in patients who have an inadequate transthoracic echo window (obesity, ventilated patients), in complicated valvular patients (especially aortic, mitral, and mechanical valves), in suspected endocarditis, in congenital heart disease, or to exclude a thrombus in the left atrial appendage in patients with AF.

Stress echocardiography

Stress echocardiography (dobutamine or exercise echo) is used to detect ventricular dysfunction caused by ischaemia and to assess myocardial viability in the presence of marked hypokinesis or akinesis. It may also be useful in identifying myocardial stunning, hibernation, and in relating HF symptoms to valvular abnormalities. In patients with HF, stress echo may have a lower sensitivity and specificity due to LV dilatation or the presence of bundle branch block.

Additional non-invasive imaging tests

In patients in whom echocardiography at rest has not provided adequate information and in patients with suspected CAD, further non-invasive imaging may include cardiac magnetic resonance imaging (CMR), cardiac CT, or radionuclide imaging.

Cardiac magnetic resonance imaging (CMR)

CMR is a versatile, highly accurate, reproducible, non-invasive imaging technique for the assessment of left and right ventricular volumes, global function, regional wall motion, myocardial thickness, thickening, myocardial mass and tumours, cardiac valves, congenital defects, and pericardial disease.[65,66] It has become the gold standard of accuracy and reproducibility for assessment of volumes, mass, and wall motion. The use of paramagnetic contrast agents such as gadolinium can provide evidence of inflammation, infiltration, and scarring in patients with infarction, myocarditis, pericarditis, cardiomyopathies, infiltrative and storage diseases. Limitations include cost, availability, patients with dysrhythmia or an implanted device and patient intolerance.

CT scan

In patients with HF, non-invasive diagnosis of coronary anatomy might be of value and assist in decisions concerning coronary

angiography. CT angiography may be considered in patients with a low or intermediate pre-test probability of CAD and an equivocal exercise or imaging stress test.[66] The demonstration of atherosclerosis on a CT scan confirms CAD but does not necessarily imply ischaemia.

Radionuclide ventriculography

Radionuclide ventriculography is recognized as a relatively accurate method of determining LVEF and is most often performed in the context of a myocardial perfusion scan providing information on viability and ischaemia. It has limited value for assessing volumes or more subtle indices of systolic or diastolic function.

Pulmonary function tests

Measurements of pulmonary function are of limited value in the diagnosis of HF. However, these tests are useful in demonstrating or excluding respiratory causes of breathlessness and assessing the potential contribution of lung disease to the patient's dyspnoea. Routine spirometry evaluates the extent of obstructive airways disease. The presence of pulmonary congestion may influence the test results. Blood gases are normal in well-compensated chronic HF. A reduction of arterial oxygen saturation should lead to a search for other diagnoses.

Exercise testing

Exercise testing is useful for the objective evaluation of exercise capacity and exertional symptoms, such as dyspnoea and fatigue. The 6-min walk test is a simple, reproducible, readily available tool frequently employed to assess submaximal functional capacity and evaluate the response to intervention. A normal peak exercise test in a patient not receiving treatment excludes the diagnosis of symptomatic HF. Either a cycle ergometer or treadmill may be used with a modified HF protocol employing a slow increase in workload. Gas exchange analysis during exercise is preferable as it provides a highly reproducible measurement of exercise limitation and insights into the differentiation between cardiac or respiratory cause of dyspnoea, assesses ventilatory efficiency, and carries prognostic information. Peak oxygen uptake (peak VO_2) and the anaerobic threshold are useful indicators of the patient's functional capacity, and peak VO_2 and the VE/VCO_2 slope (ventilatory response to exercise) is a major prognostic variable. The peak respiratory exchange ratio is a useful index of the degree of anaerobiosis achieved. There is a poor correlation between exercise capacity, EF, and most haemodynamic measures at rest.

Ambulatory ECG monitoring (Holter)

Ambulatory ECG monitoring is valuable in the assessment of patients with symptoms suggestive of an arrhythmia (e.g. palpitations or syncope) and in monitoring ventricular rate control in patients with AF. It may detect and quantify the nature, frequency, and duration of atrial and ventricular arrhythmias and silent episodes of ischaemia which could be causing or exacerbating symptoms of HF. Episodes of symptomatic, non-sustained ventricular tachycardia (VT) are frequent in HF and are associated with a poor prognosis.

Cardiac catheterization

Cardiac catherization is unnecessary for the routine diagnosis and management of patients with HF. Invasive investigation is frequently indicated to elucidate aetiology, to obtain important prognostic information, and if revascularization is being considered.

Coronary angiography

Coronary angiography should be considered in HF patients with a history of exertional angina or suspected ischaemic LV dysfunction, following cardiac arrest, and in those with a strong risk factor profile for coronary heart disease, and may be urgently required in selected patients with severe HF (shock or acute pulmonary oedema) and in patients not responding adequately to treatment. Coronary angiography and LV ventriculography are also indicated in patients with refractory HF of unknown aetiology and in patients with evidence of severe mitral regurgitation or aortic valve disease potentially correctable by surgery.

Right heart catheterization

Right heart catheterization provides valuable haemodynamic information regarding filling pressures, vascular resistance and cardiac output. Its role in the diagnosis of HF is, in clinical practice, limited. It forms the basis for the Forrester classification and is the most accurate method to evaluate haemodynamics in patients refractory to treatment, prior to cardiac transplantation, or in clinical research evaluating interventions.

Monitoring of haemodynamic variables by means of a pulmonary arterial catheter (PAC) may be considered in hospitalized patients with cardiogenic/non-cardiogenic shock or to monitor treatment in patients with severe HF not responding to appropriate treatment. However, the use of a PAC has not been shown to improve outcomes.

Endomyocardial biopsy

Specific myocardial disorders may be diagnosed by endomyocardial biopsy (EMB). Clinical decisions must be made from available case-controlled studies and expert opinion statements. A recently published AHA/ACC/ESC joint statement for the indications of EMB[67] suggested that the procedure should be considered in patients with acute or fulminant HF of unknown aetiology who deteriorate rapidly with ventricular arrhythmias and/or AV heart block, or in patients who are unresponsive to conventional HF therapy. EMB might be also considered in chronic HF with suspected infiltrative processes such as amyloid, sarcoid, and haemochromatosis, as well as in eosinophilic myocarditis and restrictive cardiomyopathy of unknown origin.

Prognosis

Determining prognosis in HF is complex. Diverse aetiologies, age, frequent co-morbidities, variation in individual progression and outcomes (sudden vs. progressive HF death) must be considered. The impact on prognosis of specific treatments in individual patients with HF is often difficult to predict. The variables most

consistently cited as independent outcome predictors are reported in *Table 17*.

Non-pharmacological management

Self-care management

- Self-care management is a part of successful HF treatment and can significantly impact on symptoms, functional capacity, well-being, morbidity, and prognosis. Self-care can be defined as actions aimed at maintaining physical stability, avoidance of behaviour that can worsen the condition, and detection of the early symptoms of deterioration.[68]
- Important self-care behaviours in heart failure are presented in *Table 18*.
- It is recommended that healthcare professionals provide comprehensive heart failure education and counselling.

The webpage *heartfailurematters.org* represents an internet tool provided by the Heart Failure Association of the ESC that permits patients, their next of kin, and caregivers to obtain useful, practical information in a user-friendly format.

The following management options are considered appropriate in patients with symptomatic HF. The recommendations largely represent expert consensus opinion without adequate documented evidence.

Adherence to treatment

Key evidence

Good adherence has been shown to decrease morbidity and mortality and improve well-being.[69] The literature suggests that only 20–60% of patients with HF adhere to their prescribed pharmacological and non-pharmacologic treatment.[70,71] Data from the Euro-Heart Failure Survey demonstrate that a large proportion of patients either misunderstood or had problems recalling that they had received recommendations regarding self-care management such as instructions on medications or diet.[72]

- A strong relationship between healthcare professionals and patients as well as sufficient social support from an active social network has been shown to improve adherence to treatment. It is recommended that family members be invited to participate in education programmes and decisions regarding treatment and care.[73]
- Patients should have adequate knowledge of their medical treatment, especially regarding effects, side effects, and how the medication should be taken and titrated. This may be challenging in patients with cognitive dysfunction.[74]
- Patients should be aware that the beneficial effects of therapy may be delayed and not have unrealistic expectations regarding the initial response to treatment. It must be explained that side

Table 17 Conditions associated with a poor prognosis in heart failure

Demographics	Clinical	Electrophysiological	Functional/ exertional	Laboratory	Imaging
Advanced age*	**Hypotension***	**Tachycardia Q waves**	**Reduced work, low peak VO_2***	**Marked elevation of BNP/NT pro-BNP***	**Low LVEF***
Ischaemic aetiology*	**NYHA functional class III–IV***	**Wide QRS***		**Hyponatraemia***	
Resuscitated sudden death*	**Prior HF hospitalization***	**LV hypertrophy Complex ventricular arrhythmias***		**Elevated troponin* Elevated biomarkers, neurohumoral activation***	
Poor compliance	Tachycardia	Low heart rate variability Atrial fibrillation	Poor 6 min walk distance	Elevated creatinine/BUN	Increased LV volumes
Renal dysfunction	Pulmonary rales	T-wave alternans	High VE/VCO_2 slope	Elevated bilirubin Anaemia	Low cardiac index
Diabetes	Aortic stenosis		Periodic breathing	Elevated uric acid	High LV filling pressure
Anaemia	Low body mass index				Restrictive mitral filling pattern, pulmonary hypertension
COPD	Sleep-related breathing disorders				Impaired right ventricular function
Depression					

* = powerful predictors.

Table 18 Essential topics in patient education with associated skills and appropriate self-care behaviours

Educational topics	Skills and self-care behaviours
Definition and aetiology of heart failure	Understand the cause of heart failure and why symptoms occur
Symptoms and signs of heart failure	Monitor and recognize signs and symptoms Record daily weight and recognize rapid weight gain Know how and when to notify healthcare provider Use flexible diuretic therapy if appropriate and recommended
Pharmacological treatment	Understand indications, dosing, and effects of drugs Recognize the common side-effects of each drug prescribed
Risk factor modification	Understand the importance of smoking cessation Monitor blood pressure if hypertensive Maintain good glucose control if diabetic Avoid obesity
Diet recommendation	Sodium restriction if prescribed Avoid excessive fluid intake Modest intake of alcohol Monitor and prevent malnutrition
Exercise recommendations	Be reassured and comfortable about physical activity Understand the benefits of exercise Perform exercise training regularly
Sexual activity	Be reassured about engaging in sex and discuss problems with healthcare professionals Understand specific sexual problems and various coping strategies
Immunization	Receive immunization against infections such as influenza and pneumococcal disease
Sleep and breathing disorders	Recognize preventive behaviour such as reducing weight of obese, smoking cession, and abstinence from alcohol Learn about treatment options if appropriate
Adherence	Understand the importance of following treatment recommendations and maintaining motivation to follow treatment plan
Psychosocial aspects	Understand that depressive symptoms and cognitive dysfunction are common in patients with heart failure and the importance of social support Learn about treatment options if appropriate
Prognosis	Understand important prognostic factors and make realistic decisions Seek psychosocial support if appropriate

effects are often transient, and it might take months to uptitrate and assess the full effects of a drug.

- Interventions to improve adherence are recommended and should be targeted by the healthcare provider.

Class of recommendation I, level of evidence C

Symptom recognition

The symptoms of deterioration in HF may vary considerably.[75,76]

Patients and/or caregivers should learn to recognize the symptoms of deterioration and take appropriate action such as increasing the prescribed diuretic dose and/or contact the healthcare team.

- Flexible dosage of diuretics based on symptoms and fluid balance should be recommended, within pre-specified limits, after detailed instructions and education.

Class of recommendation I, level of evidence C

Weight monitoring

Increases in body weight are often associated with deterioration of HF and fluid retention.[76] Patients should be aware that deterioration without weight gain can occur.[77]

- Patients should weigh themselves on a regular basis to monitor weight change, preferably as part of a regular daily routine. In the case of a sudden unexpected weight gain of >2 kg in 3 days, patients may increase their diuretic dose and should alert the healthcare team. The risks of volume depletion with excessive diuretic use must be explained.

Class of recommendation I, level of evidence C

Diet and nutrition

Sodium intake

Sodium restriction is recommended in symptomatic HF to prevent fluid retention. Although no specific guidelines exist, excessive intake of salt should be avoided. Patients should be educated concerning the salt content of common foods.

Class of recommendation IIa, level of evidence C

Fluid intake

Fluid restriction of 1.5–2 L/day may be considered in patients with severe symptoms of HF especially with hyponatraemia. Routine fluid restriction in all patients with mild to moderate symptoms does not appear to confer clinical benefit.[78]

Class of recommendation IIb, level of evidence C

Alcohol

Alcohol may have a negative inotropic effect, and may be associated with an increase in blood pressure (BP) and the risk of arrhythmias. Excessive use may be deleterious.

- Alcohol intake should be limited to 10–20 g/day (1–2 glasses of wine/day).

Class of recommendation IIa, level of evidence C

- Patients suspected of having alcohol-induced cardiomyopathy should abstain from alcohol completely.[79]

Class of recommendation I, level of evidence C

Weight reduction

Weight reduction in obese [body mass index (BMI) $>30\ kg/m^2$] persons with HF should be considered in order to prevent the progression of HF, decrease symptoms, and improve well-being.

Class of recommendation IIa, level of evidence C

In moderate to severe HF, weight reduction should not routinely be recommended since unintentional weight loss and anorexia are common problems.

Unintentional weight loss

Clinical or subclinical malnutrition is common in patients with severe HF. The pathophysiology of cardiac cachexia in heart failure is complex and not completely understood, but altered metabolism, insufficient food intake, decreased nutritional uptake, gut congestion and inflammatory mechanisms may be important factors. Cardiac cachexia is an important predictor of reduced survival.[80]

- If weight loss during the last 6 months is >6% of previous stable weight without evidence of fluid retention, the patient is defined as cachectic.[81] The patient's nutritional status should be carefully assessed.

Class of recommendation I, level of evidence C

Smoking

Smoking is a known risk factor for cardiovascular disease. No prospective studies have evaluated effects of smoking cessation in patients with HF. Observational studies support the relationship between smoking cessation and decreased morbidity and mortality.[82,83]

- It is recommended that patients receive support and advice and be motivated to stop smoking.

Class of recommendation I, level of evidence C

Immunization

- Pneumoccocal vaccination and annual influenza vaccination should be considered in patients with symptomatic HF without known contraindications.[84]

Class of recommendation IIa, level of evidence C

Activity and exercise training

Physical inactivity is common in patients with symptomatic HF and contributes to its progression.[85] Regular, initially supervised, resistance or endurance physical training improves autonomic control by enhancing vagal tone and reducing sympathetic activation, improves muscle strength, vasodilator capacity, and endothelial dysfunction, and decreases oxidative stress. Several systematic reviews and meta-analyses of small studies have shown that physical conditioning by exercise training reduces mortality and hospitalization when compared with usual care alone, and improves exercise tolerance and health-related quality of life.[86–90] Cardiac rehabilitation programmes following a cardiovascular event or episode of decompensation represent an effective treatment option for patients with HF.

- Regular, moderate daily activity is recommended for all patients with heart failure.

Class of recommendation I, level of evidence B

- Exercise training is recommended, if available, to all stable chronic HF patients. There is no evidence that exercise training should be limited to any particular HF patient subgroups (aetiology, NYHA class, LVEF, or medication). Exercise training programmes appear to have similar effects whether provided in a hospital or at home.

Class of recommendation I, level of evidence A

Sexual activity

Sexual problems related to cardiovascular disease, medical treatment (β-blockers), or psychological factors such as fatigue and depression are common in patients with HF. There is limited evidence regarding the influence of sexual activity on clinical status in patients with mild or moderate symptoms. A slightly increased risk of decompensation triggered by sexual activity in patients in NYHA class III–IV has been reported. Cardiovascular symptoms such as dyspnoea, palpitations, or angina during sex rarely occur in patients who do not experience similar symptoms during exercise levels representing moderate exertion.[91]

Patients may be advised to use sublingual nitroglycerine as prophylaxis against dyspnoea and chest pain during sexual activity.

- Phosphodiesterase 5 (PDE5) inhibitors (e.g. sildenafil) reduce pulmonary pressures but are not currently recommended for patients with advanced HF. They should never be used in combination with nitrate preparations.

Class of recommendation III, level of evidence B

- Individualized sensitive counselling is recommended for both male and female patients and their partners.

Class of recommendation I, level of evidence C

Pregnancy and contraception

- Pregnancy may lead to deterioration of HF due to the rise in blood volume and increase in cardiac output, as well as the substantial increase in extravascular fluid. Importantly, many medications used in HF treatment are contraindicated during pregnancy.
- The risk of pregnancy is considered greater than the risks linked to contraceptive use. It is recommended that women with heart failure discuss contraceptives and planned pregnancy with a physician in order to take an informed decision based on assessment of potential risks.

Travelling

High altitudes (>1500 m) and travel to very hot and humid destinations should be discouraged for symptomatic patients. Planned travel should be discussed with the HF team. As a rule, air travel is preferable to long journeys by other means of transportation.

Sleep disorders

Patients with symptomatic HF frequently have sleep-related breathing disorders (central or obstructive sleep apnoea). These

conditions may be associated with increased morbidity and mortality.[92]

- Weight loss in severely overweight persons, smoking cessation, and abstinence of alcohol can reduce risk and is recommended.

Class of recommendation I, level of evidence C

- Treatment with a continuous positive airway pressure (CPAP) should be considered in obstructive sleep apnoea documented by polysomnography.[93]

Class of recommendation IIa, level of evidence C

Depression and mood disorders

The prevalence of clinically significant depression has been found to be as high as 20% in HF patients and may be much higher in patients screened with more sensitive instruments or in patients with more advanced HF. Depression is associated with increased morbidity and mortality.[94]

- There is limited evidence regarding screening and assessment tools as well as of the efficacy of psychological and pharmacological interventions in patients with HF. However, screening for depression and initiating appropriate treatment should be considered in patients with suggestive symptoms.

Class of recommendation IIa, level of evidence C

Prognosis

Although challenging to discuss, it is important that patients understand the important prognostic factors. Recognition of the impact of treatment on prognosis may motivate patients to adhere to treatment recommendations. An open discussion with the family may assist in making realistic and informed decisions regarding treatment and future plans.

Pharmacological therapy

Objectives in the management of heart failure

The purpose of diagnosing and treating HF is no different from any other medical condition, namely to bring about a reduction of mortality and morbidity (*Table 19*). Since the annual mortality of HF is so high, particular emphasis has been put on this end-point in clinical trials. However, for many patients, and notably the elderly, the ability to lead an independent life, freedom from excessively unpleasant symptoms, and avoidance of admission to hospital are goals which on occasion may be equivalent to the desire to maximize the duration of life. Prevention of heart disease or its progression remains an essential part of management. Many of the randomized clinical trials in HF have evaluated patients with systolic dysfunction based on an EF $<35–40\%$. This is a relatively arbitrary cut-off level and there is limited evidence in the large population with symptomatic HF and an EF between 40 and 50%.

Figure 2 provides a treatment strategy for the use of drugs and devices in patients with symptomatic HF and systolic dysfunction. It is essential to detect and consider treatment of the common cardiovascular and non-cardiovascular co-morbidities.

Table 19 Objectives of treatment in chronic heart failure

1. Prognosis	Reduce mortality
2. Morbidity	Relieve symptoms and signs Improve quality of life Eliminate oedema and fluid retention Increase exercise capacity Reduce fatigue and breathlessness Reduce need for hospitalization Provide for end of life care
3. Prevention	Occurrence of myocardial damage Progression of myocardial damage Remodelling of the myocardium Reoccurrence of symptoms and fluid accumulation Hospitalization

Angiotensin-converting enzyme inhibitors (ACEIs)

Unless contraindicated or not tolerated, an ACEI should be used in all patients with symptomatic HF and a LVEF $\leq 40\%$. Treatment with an ACEI improves ventricular function and patient well-being, reduces hospital admission for worsening HF, and increases survival. In hospitalized patients, treatment with an ACEI should be initiated before discharge.

Class of recommendation I, level of evidence A

Key evidence

- Two key randomized controlled trials (RCTs) (CONSENSUS and SOLVD-Treatment) assigned ~2800 patients with mild to severely symptomatic HF to placebo or enalapril.[95,96] Most were also treated with a diuretic and digoxin, but $<10\%$ of patients in each trial were treated with a β-blocker. In CONSENSUS, which enrolled patients with severe HF, 53% of patients were treated with spironolactone.
- Each of these two RCTs showed that ACEI treatment reduced mortality [relative risk reduction (RRR) 27% in CONSENSUS and 16% in SOLVD-Treatment]. In SOLVD-Treatment there was also an RRR of 26% in hospital admission for worsening HF. These benefits were *additional* to those gained with conventional treatment.
- The absolute risk reduction (ARR) in mortality in patients with *mild or moderate HF* (SOLVD-Treatment) was 4.5% equating to a number needed to treat (NNT) of 22 to postpone one death (over an average of 41 months). The equivalent figures for *severe HF* (CONSENSUS) were ARR = 14.6% and NNT = 7 (over an average of 6 months), respectively.
- These findings are supported by a meta-analysis of smaller, short-term, placebo-controlled RCTs, which showed a clear reduction in mortality *within only 3 months*. These RCTs also showed that ACEIs improve symptoms, exercise tolerance, quality of life, and exercise performance.[97]
- In ATLAS, 3164 patients with mainly moderate to severe HF were randomized to low-or high-dose lisinopril. There was a RRR of

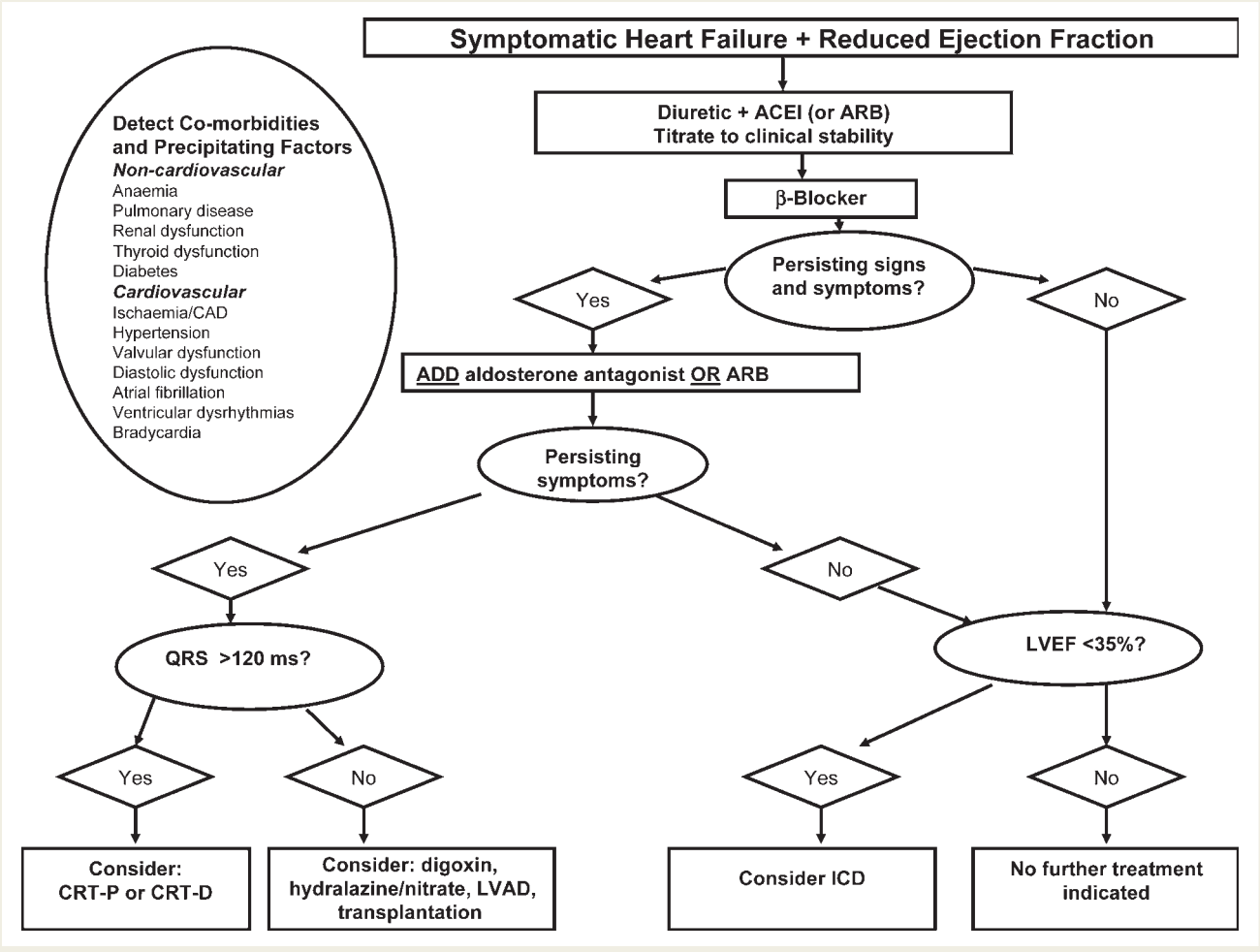

Figure 2 A treatment algorithm for patients with symptomatic heart failure and reduced ejection fraction.

15% in the risk of death or HF hospitalization in the high-dose lisinopril group as compared with the low-dose lisinopril group.[98]

- Additional support for the use of ACEIs comes from an RCT in patients with a low LVEF but no symptoms of HF ('asymptomatic LV systolic dysfunction') and three large (5966 patients in total) placebo-controlled, randomized, outcome trials in patients with HF, LV systolic dysfunction, or both after acute MI.[99] In the SOLVD-Prevention trial (which randomized 4228 patients with asymptomatic LV systolic dysfunction), there was a 20% RRR in death or HF hospitalization. In the MI trials, which used captopril (SAVE), ramipril (AIRE), and trandolapril (TRACE), there was a 26% RRR in death and 27% RRR in death or HF hospitalization. ACEIs have also been shown to reduce the risk of MI in patients with and without HF and irrespective of LVEF.
- ACEIs occasionally cause worsening of renal function, hyperkalaemia, symptomatic hypotension, cough and rarely angioedema. An ACEI should only be used in patients with adequate renal function and a normal serum potassium.[99]

Which patients should get an ACEI?

Indications, based upon the patients enrolled in the RCTs:

LVEF $\leq$40%, irrespective of symptoms.

Contraindications

- History of angioedema
- Bilateral renal artery stenosis
- Serum potassium concentration >5.0 mmol/L
- Serum creatinine >220 μmol/L (~2.5 mg/dL)
- Severe aortic stenosis

How to use an ACEI in heart failure (*Table 20*)

Initiation of an ACEI

- Check renal function and serum electrolytes
- Re-check renal function and serum electrolytes within 1–2 weeks of starting treatment.

Dose up-titration

- Consider dose up-titration after 2–4 weeks. Do not increase dose if significant worsening of renal function or hyperkalaemia. Re-check renal function and serum electrolytes 1 and 4 weeks after increasing dose. More rapid dose up-titration can be carried out in patients in hospital or otherwise closely supervised, tolerability permitting.

Table 20 Dosages of commonly used drugs in heart failure

	Starting dose (mg)		Target dose (mg)	
ACEI				
Captopril	6.25	t.i.d.	50–100	t.i.d.
Enalapril	2.5	b.i.d.	10–20	b.i.d.
Lisinopril	2.5–5.0	o.d.	20–35	o.d.
Ramipril	2.5	o.d.	5	b.i.d.
Trandolapril	0.5	o.d.	4	o.d.
ARB				
Candesartan	4 or 8	o.d.	32	o.d.
Valsartan	40	b.i.d.	160	b.i.d.
Aldosterone antagonist				
Eplerenone	25	o.d.	50	o.d.
Spironolactone	25	o.d.	25–50	o.d.
β-Blocker				
Bisoprolol	1.25	o.d.	10	o.d.
Carvedilol	3.125	b.i.d.	25–50	b.i.d.
Metoprolol succinate	12.5/25	o.d.	200	o.d.
Nebivolol	1.25	o.d.	10	o.d.

- In the absence of above problems, aim for evidence-based *target dose* or maximum tolerated dose (*Table 20*).
- Re-check renal function and serum electrolytes 1, 3, and 6 months after achieving maintenance dose and 6 monthly thereafter.

Potential adverse effects

- **Worsening renal function**—some rise in urea (blood urea nitrogen) and creatinine is expected after initiation of an ACEI and is not considered clinically important unless rapid and substantial. Check for nephrotoxic drugs such as non-steroidal anti-inflammatory drugs (NSAIDs). If necessary, reduce ACEI dose or discontinue. An increase in creatinine of up to 50% from baseline or to an absolute concentration of 265 μmol/L (~3 mg/dL), whichever is lower, is acceptable. If the creatinine rises above 265 μmol/L (~3.0 mg/dL), but below 310 μmol/L (~3.5 mg/dL), halve dose of ACEI and monitor blood chemistry closely. If creatinine rises to 310 μmol/L (~3.5 mg/dL) or above, stop ACEI immediately and monitor blood chemistry closely.
- **Hyperkalaemia**—check for use of other agents causing hyperkalaemia, e.g. potassium supplements and potassium-sparing diuretics, e.g. amiloride, and stop. If potassium rises above 5.5 mmol/L, halve dose of ACEI and monitor blood chemistry closely. If potassium rises over 6.0 mmol/L, stop ACEI immediately and monitor blood chemistry closely.
- **Symptomatic hypotension** (e.g. dizziness) is common—often improves with time, and patients should be reassured. Consider reducing the dose of diuretics and other hypotensive agents (except ARB/β-blocker/aldosterone antagonist). *Asymptomatic* hypotension does not require intervention.
- **Cough—**if an ACEI causes a troublesome cough, switch to an ARB.

β-Blockers

Unless contraindicated or not tolerated, a β-blocker should be used in all patients with symptomatic HF and an LVEF ≤40%. β-Blockade improves ventricular function and patient well-being, reduces hospital admission for worsening HF, and increases survival. Where possible, in hospitalized patients, treatment with a β-blocker should be initiated cautiously before discharge.

Class of recommendation I, level of evidence A

Key evidence

- More RCTs have been undertaken with β-blockers than with ACEIs in patients with HF.[100–104]
- Three key trials (CIBIS II, COPERNICUS, and MERIT-HF) randomized nearly 9000 patients with mild to severely symptomatic HF to placebo or a β-blocker (bisoprolol, carvedilol, or metoprolol succinate CR). More than 90% of patients were on an ACEI or ARB. Most were also treated with a diuretic and more than half with digoxin.
- Each of these three trials showed that β-blocker treatment reduced mortality (RRR ~34% in each trial) and hospital admission for worsening heat failure (RRR 28–36%) within ~1 year of starting treatment. There was also an improvement in self-reported patient well-being in COPERNICUS and MERIT-HF. These benefits were *additional* to those gained with conventional treatment, including an ACEI.
- The ARR in mortality (after 1 year of treatment) in patients with *mild to moderate HF* (CIBIS 2 and MERIT-HF combined) was 4.3%, equating to an NNT (for 1 year to postpone 1 death) of 23. The equivalent figures for *severe HF* (COPERNICUS) were ARR = 7.1% and NNT = 14, respectively.
- These findings are supported by another placebo-controlled RCT (SENIORS) in 2128 elderly (≥70 years) patients, 36% of which had a LVEF >35%. Treatment with nebivolol resulted in an RRR of 14% in the primary composite end-point of death or hospital admission for a cardiovascular reason.[105]
- The findings of these trials were also supported by an earlier programme of studies with carvedilol (US carvedilol studies), meta-analysis of other small β-blocker trials, and a placebo-controlled RCT in 1959 patients with an LVEF ≤0.40 after acute MI in which the RRR in mortality with carvedilol was 23% during a mean follow-up period of 1.3 years.[103]
- One large RCT (BEST) with bucindolol, a β-blocker with partial agonist properties, did not show a significant reduction in mortality, though its findings were generally consistent with the above studies.[106]
- Another RCT, COMET, showed that carvedilol increased survival compared with short-acting metoprolol tartrate (different from the long-acting succinate formulation used in MERIT-HF).[107]
- β-Blockers should usually be initiated in stable patients and only with caution in recently decompensated patients (and only initiated in hospital in these patients). Recently decompensated patients were, however, safely initiated on β-blocker treatment in COPERNICUS.

- In patients admitted to hospital due to worsening HF, a reduction in the β-blocker dose may be necessary. In severe situations, temporary discontinuation can be considered. Low-dose therapy should be re-instituted and up-titrated as soon as the patient's clinical condition permits, preferably prior to discharge.

Which patients should get a β-blocker?

Indications, based upon patients enrolled in the RCTs:

- LVEF ≤40%.
- Mild to severe symptoms (NYHA functional class II–IV); patients with asymptomatic LV systolic dysfunction after MI also have an indication for a β-blocker.
- Optimal dose level of an ACEI or/and ARB (and aldosterone antagonist, if indicated).
- Patients should be clinically stable (e.g. no recent change in dose of diuretic). Cautious, pre-discharge, initiation is possible in a recently decompensated patient provided that the patient has improved with other treatments, is not dependent on an i.v. inotropic agent, and can be observed in hospital for at least 24 h after initiation of β-blocker treatment.

Contraindications

- Asthma [chronic obstructive pulmonary disease (COPD) is not a contraindication].
- Second- or third-degree heart block, sick sinus syndrome (in the absence of a permanent pacemaker), sinus bradycardia (<50 b.p.m.).

How to use a β-blocker in heart failure (*Table 20*)

Initiation of a β-blocker

- *Starting dose*: bisoprolol 1.25 mg o.d., carvedilol 3.125–6.25 mg b.i.d., metoprolol CR/XL 12.5–25 mg o.d., or nebivolol 1.25 mg o.d.—under supervision in outpatient setting.
- β-Blockers may be initiated prior to hospital discharge in recently decompensated patients with caution.

Dose up-titration

- Visits every 2–4 weeks to up-titrate the dose of β-blocker (slower dose up-titration may be needed in some patients). Do not increase dose if signs of worsening HF, symptomatic hypotension (e.g. dizziness), or excessive bradycardia (pulse rate <50/min) at each visit.
- In absence of the above problems, double the dose of β-blocker at each visit until the evidence-based *target dose* is reached—bisoprolol 10 mg o.d., carvedilol 25–50 mg b.i.d., metoprolol CR/XL 200 mg o.d., or nebivolol 10 mg o.d.—or maximum tolerated dose.

Potential adverse effects

- **Symptomatic hypotension**—often improves with time; consider reducing dose of other hypotensive agents (except ACEI/ARB), e.g. diuretics, nitrates. *Asymptomatic* hypotension does not require intervention.
- **Worsening HF**—increase dose of diuretic (often only temporary requirement) and continue β-blocker (often at a lower dose) if possible.
- **Excessive bradycardia**—record ECG (or perform ambulatory monitoring when necessary) to exclude heart block. Consider stopping digitalis glycoside if administered. The dose of β-blocker may need to be reduced or the treatment discontinued.

Aldosterone antagonists

Unless contraindicated or not tolerated, the addition of a low-dose of an aldosterone antagonist should be considered in all patients with an LVEF ≤35% and severe symptomatic HF, i.e. currently NYHA functional class III or IV, in the absence of hyperkalaemia and significant renal dysfunction. Aldosterone antagonists reduce hospital admission for worsening HF and increase survival when added to existing therapy, including an ACEI. In hospitalized patients satisfying these criteria, treatment with an aldosterone antagonist should be initiated before discharge.

Class of recommendation I, level of evidence B

Key evidence

- A single large RCT (RALES) has been undertaken with the aldosterone antagonist spironolactone in patients with severe HF.[108]
- In RALES 1663 patients with an LVEF ≤35% and in NYHA functional class III (having been in class IV within the past 6 months) were randomized to placebo or spironolactone 25–50 mg o.d. added to conventional treatment, including a diuretic, ACEI (95%), and digoxin (74%). At the time this trial was conducted, β-blockers were not widely used to treat HF, and only 11% were treated with a β-blocker.
- Treatment with spironolactone led to an RRR in death of 30% and an RRR in hospital admission for worsening HF of 35% within an average of 2 years of starting treatment. Spironolactone also improved NYHA class. These benefits were *additional* to those gained with conventional treatment, including an ACEI.
- The ARR in mortality (after a mean of 2 years of treatment) in patients with *severe HF* was 11.4%, equating to an NNT (for 2 years to postpone 1 death) of 9.
- These findings are supported by another RCT (EPHESUS) which enrolled 6632 patients 3–14 days after acute MI with an LVEF ≤40% and HF or diabetes.[109] Patients were randomized to placebo or eplerenone 25–50 g o.d. added to conventional treatment including an ACEI/ARB (87%) and β blocker (75%). Treatment with eplerenone led to an RRR in death of 15%.
- Spironolactone and eplerenone can cause hyperkalaemia and worsening renal function, which were uncommon in the RCTs but may occur more frequently in ordinary clinical practice, especially in the elderly. Both should only be used in patients with adequate renal function and a normal serum potassium

concentration; if either is used, serial monitoring of serum electrolytes and renal function is mandatory.[110]
- Spironolactone can also cause breast discomfort and enlargement in men (10% compared with placebo, in RALES); this side effect is infrequent with eplerenone. Outside the post-infarction indication, the main indication for eplerenone is in men with breast discomfort and/or enlargement caused by spironolactone.

Patients who should get an aldosterone antagonist
Indications, based upon the RCT:

- LVEF ≤35%.
- Moderate to severe symptoms (NYHA functional class III–IV).
- Optimal dose of a β-blocker and an ACEI or an ARB (but not an ACEI and an ARB).

Contraindications

- Serum potassium concentration >5.0 mmol/L
- Serum creatinine >220 μmol/L (~2.5 mg/dL)
- Concomitant potassium sparing diuretic or potassium supplements
- Combination of an ACEI and ARB

How to use spironolactone (or eplerenone) in heart failure (*Table 20*)
Initiation of spironolactone (or eplerenone)

- Check renal function and serum electrolytes.
- *Starting dose*: spironolactone 25 mg o.d. (or eplerenone 25 mg o.d.).
- Re-check renal function and serum electrolytes 1 and 4 weeks after starting treatment.

Dose up-titration

- Consider dose up-titration after 4–8 weeks. Do not increase dose if worsening renal function or hyperkalaemia. Re-check renal function and serum electrolytes 1 and 4 weeks after increasing dose.
- In absence of above problems, aim for evidence-based *target dose*—spironolactone 50 mg o.d. or eplerenone 50 mg o.d.—or maximum tolerated dose.
- Re-check renal function and serum electrolytes 1, 2, 3, and 6 months after achieving maintenance dose, and 6 monthly thereafter.

Potential adverse effects

- **Hyperkalaemia**—if potassium rises to >5.5 mmol/L, halve dose of spironolactone (or eplerenone), e.g. to 25 mg on alternate days, and monitor blood chemistry closely. If potassium rises to 6.0 mmol/L stop spironolactone (or eplerenone) immediately and monitor blood chemistry closely; specific treatment of hyperkalaemia may be needed.
- **Worsening renal function**—if creatinine rises to >220 μmol/L (~2.5 mg/dL) halve dose of spironolactone (or eplerenone), e.g. to 25 mg on alternate days, and monitor blood chemistry closely. If creatinine rises to >310 μmol/L (~3.5 mg/dL) stop spironolactone (or eplerenone) immediately and monitor blood chemistry closely; specific treatment of renal dysfunction may be needed.
- **Breast tenderness and/or enlargement**—switch from spironolactone to eplerenone.

Angiotensin receptor blockers (ARBs)

Unless contraindicated or not tolerated, an ARB is recommended in patients with HF and an LVEF ≤40% who remain symptomatic despite optimal treatment with an ACEI and β-blocker, unless also taking an aldosterone antagonist. Treatment with an ARB improves ventricular function and patient well-being, and reduces hospital admission for worsening HF.

Class of recommendation I, level of evidence A

Treatment reduces the risk of death from cardiovascular causes.

Class of recommendation IIa, level of evidence B

- An ARB is recommended as an alternative in patients intolerant of an ACEI. In these patients, an ARB reduces the risk of death from a cardiovascular cause or hospital admission for worsening HF. In hospitalized patients, treatment with an ARB should be initiated before discharge.

Class of recommendation I, level of evidence B

Key evidence

- Two key placebo-controlled RCTs (Val-HEFT and CHARM-Added) randomized ~7600 patients with mild to severely symptomatic HF to placebo or an ARB (valsartan and candesartan), added to an ACEI (in 93% of patients in Val-HeFT and all in CHARM-Added).[111,112] In addition, 35% of patients in Val-HeFT and 55% in CHARM-Added were treated with a β-blocker. Five per cent of patients in Val-HeFT and 17% in CHARM-Added were treated with spironolactone.
- Each of these two trials showed that ARB treatment reduced the risk of hospital admission for worsening HF (RRR 24% in Val-HeFT and 17% in CHARM-Added) but not all-cause hospitalization. There was a 16% RRR in the risk of death from a cardiovascular cause with candesartan in CHARM-Added. These benefits were *additional* to those gained with conventional treatment, including a diuretic, digoxin, an ACEI, and a β-blocker.
- The ARR in the primary composite mortality–morbidity endpoint in patients with *mild to moderate HF* was 4.4%, equating to an NNT (for an average of 41 months to postpone 1 event) of 23 in CHARM-Added. The equivalent figures for Val-HeFT were ARR = 3.3% and NNT = 30 (over an average of 23 months), respectively.
- The CHARM trials and Val-HeFT also showed that ARBs improve symptoms and quality of life. Other trials showed that these agents improve exercise capacity.
- CHARM-Alternative was a placebo-controlled RCT with candesartan in 2028 patients with a LVEF ≤40%, intolerant

of an ACEI.[113] Treatment with candesartan resulted in an RRR of death from a cardiovascular cause or hospital admission for worsening HF of 23% (ARR = 7%, NNT = 14, over 34 months of follow-up).
- Additional support for the use of ARBs comes from VALIANT,[114] an RCT in which 14 703 patients with HF, LV systolic dysfunction, or both after acute MI were assigned to treatment with captopril, valsartan, or the combination. Valsartan was found to be non-inferior to captopril. A similar trial with losartan (OPTIMAAL) did not demonstrate non-inferiority as compared with captopril.[115,116]

Patients who should get an angiotensin receptor blocker
Indications, based upon the patients enrolled in the RCTs:

- LVEF ≤40% and either
- as an alternative in patients with mild to severe symptoms (NYHA functional class II–IV) who are intolerant of an ACEI
- or in patients with persistent symptoms (NYHA functional class II–IV) despite treatment with an ACEI and β-blocker
- ARBs may cause worsening of renal function, hyperkalaemia, and symptomatic hypotension with an incidence similar to an ACEI. They do not cause cough.

Contraindications

- As with ACEIs, with the exception of angioedema
- Patients treated with an ACEI *and* an aldosterone antagonist
- An ARB should only be used in patients with adequate renal function and a normal serum potassium concentration; serial monitoring of serum electrolytes and renal function is mandatory, especially if an ARB is used in conjunction with an ACEI.

How to use an angiotensin receptor blocker in heart failure (*Table 20*)
Initiation of an ARB

- Check renal function and serum electrolytes
- *Starting dose:* either candesartan 4–8 mg o.d. or valsartan 40 mg b.i.d.
- Re-check renal function and serum electrolytes within 1 week of starting treatment.

Dose up-titration

- Consider dose up-titration after 2–4 weeks. Do not increase dose if worsening renal function or hyperkalaemia. Re-check renal function and serum electrolytes 1 and 4 weeks after increasing dose.
- In absence of above problems, aim for evidence-based *target dose*—candesartan 32 mg o.d. or valsartan 160 mg b.i.d.—or maximum tolerated dose.
- Re-check renal function and serum electrolytes 1, 3, and 6 months after achieving maintenance dose, and 6 monthly thereafter.

Potential adverse effects

- As with ACEIs except for cough.

Hydralazine and isosorbide dinitrate (H-ISDN)

In symptomatic patients with an LVEF ≤40%, the combination of H-ISDN may be used as an *alternative* if there is intolerance to both an ACEI and an ARB. *Adding* the combination of H-ISDN should be considered in patients with persistent symptoms despite treatment with an ACEI, β-blocker, and an ARB or aldosterone antagonist. Treatment with H-ISDN in these patients may reduce the risk of death.

Class of recommendation IIa, level of evidence B

Reduces hospital admission for worsening HF.

Class of recommendation IIa, level of evidence B

Improves ventricular function and exercise capacity.

Class of recommendation IIa, level of evidence A

Key evidence

- There are two placebo-controlled (V-HeFT-I and A-HeFT) RCTs and one active-controlled (V-HeFT-II) RCT with H-ISDN.[117–119]
- In V-HeFT-I, 642 men were randomized to placebo, prazosin, or H-ISDN added to a diuretic and digoxin. No patients were treated with a β-blocker or an ACEI. Mortality was not different in the placebo and prazosin groups. With H-ISDN, there was a trend to a reduction in all-cause mortality during the overall period of follow-up (mean 2.3 years): RRR 22%; ARR 5.3%; NNT = 19. H-ISDN increased exercise capacity and LVEF compared with placebo.
- In A-HeFT, 1050 African-American men and women in NYHA class III or IV, were randomized to placebo or H-ISDN, added to a diuretic (in 90%), digoxin (60%), an ACEI (70%), an ARB (17%), a β-blocker (74%), and spironolactone (39%). The trial was discontinued prematurely, after a median follow-up of 10 months, because of a significant reduction in mortality (RRR 43%; ARR 4.0%; NNT = 25). H-ISDN also reduced the risk of HF hospitalization (RRR 33%) and improved quality of life.
- In V-HeFT-II, 804 men, in mainly NYHA class II and III, were randomized to enalapril or H-ISDN, added to a diuretic and digoxin. No patients were treated with a β-blocker. There was a trend in the H-ISDN group to an increase in all-cause mortality during the overall period of follow-up (mean 2.5 years): relative increase in risk 28%.
- The most common adverse effects with H-ISDN in these trials were headache, dizziness/hypotension, and nausea. Arthralgia leading to discontinuation or reduction in dose of H-ISDN occurred in ~5–10% of patients in V-HeFT I and II and sustained increase in antinuclear antibody (ANA) in 2–3% of patients (but lupus-like syndrome was rare).

Patients who should get hydralazine and isosorbide dinitrate
Indications, based upon the patients enrolled in the RCTs

- An alternative to an ACEI/ARB when both of the latter are not tolerated
- As add-on therapy to an ACEI if an ARB or aldosterone antagonist is not tolerated
- Evidence is strongest in patients of African-American descent

Contraindications

- Symptomatic hypotension
- Lupus syndrome
- Severe renal failure (dose reduction may be needed)

How to use hydralazine and isosorbide dinitrate in heart failure

Initiation

- *Starting dose*: hydralazine 37.5 mg and ISDN 20 mg t.i.d.

Dose up-titration

- Consider dose up-titration after 2–4 weeks. Do not increase dose with symptomatic hypotension.
- If tolerated, aim for evidence-based *target dose*—hydralazine 75 mg and ISDN 40 mg t.i.d.—or maximum tolerated dose.

Potential adverse effects

- Symptomatic hypotension (e.g. dizziness)—often improves with time; consider reducing dose of other hypotensive agents (except ACEI/ARB/β-blocker/aldosterone antagonist). Asymptomatic hypotension does not require intervention.
- Arthralgia/muscle aches, joint pain or swelling, pericarditis/pleuritis, rash or fever—consider drug-induced lupus-like syndrome; check ANA, discontinue H-ISDN.

Digoxin

In patients with symptomatic HF and AF, digoxin may be used to slow a rapid ventricular rate. In patients with AF and an LVEF ≤40% it should be used to control heart rate in addition to, or prior to a β-blocker.

Class of recommendation I, level of evidence C

In patients in sinus rhythm with symptomatic HF and an LVEF ≤40%, treatment with digoxin (in addition to an ACEI) improves ventricular function and patient well-being, reduces hospital admission for worsening HF, but has no effect on survival.

Class of recommendation IIa, level of evidence B

Key evidence

Digoxin in patients with HF and atrial fibrillation

- Digoxin is useful for initial control of the ventricular rate in a patient with rapid AF and may be considered in decompensated HF patients prior to initiation of a β-blocker.
- In the longer term, a β-blocker, either alone or in combination with digoxin, is the preferred treatment for rate control (and other clinical outcome benefits) in patients with an LVEF ≤40%.
- While digoxin alone may control the ventricular rate at rest (target <80 b.p.m.), it does not usually provide sufficient rate control during exercise (target heart rate ≤110–120 b.p.m.).
- In patients with an LVEF >40%, verapamil or diltiazem may be used alone or in combination with digoxin to control the ventricular rate.

Digoxin in patients with HF, LVEF ≤40%, and sinus rhythm

- A single large prospective outcome RCT has been undertaken with digoxin in patients with symptomatic HF and a low LVEF.
- In the DIG trial, 6800 patients with an LVEF ≤45% and in NYHA functional class II–IV were randomized to placebo or digoxin (0.25 mg o.d), added to a diuretic and ACEI. This trial was performed before β-blockers were widely used for HF.[120]
- Treatment with digoxin did not alter all-cause mortality but did lead to an RRR for hospital admission for worsening HF of 28% within an average of 3 years of starting treatment. The absolute ARR was 7.9%, equating to an NNT (for 3 years to postpone 1 patient admission) of 13.
- These findings are supported by a meta-analysis,[121] but not supported entirely by the DIG trial where quality of life was not improved[122] and there was no advantage in patients with HFPEF.
- Digoxin can cause atrial and ventricular arrhythmias, particularly in the context of hypokalaemia, and serial monitoring of serum electrolytes and renal function is mandatory.

Patients with heart failure who should get digoxin

Indications, based upon patients enrolled in the RCTs:

Atrial fibrillation

- With ventricular rate at rest >80 b.p.m., at exercise >110–120 b.p.m.

Sinus rhythm

- LV systolic dysfunction (LVEF ≤40%)
- Mild to severe symptoms (NYHA functional class II–IV)
- Optimal dose of ACEI or/and an ARB, β-blocker and aldosterone antagonist, if indicated

Contraindications

- Second- or third-degree heart block (without a permanent pacemaker); caution if suspected sick sinus syndrome
- Pre-excitation syndromes
- Previous evidence of digoxin intolerance

How to use digoxin in heart failure

Initiation of digoxin

- *Starting dose*: loading doses of digoxin are generally not required in stable patients with sinus rhythm. A single daily maintenance dose of 0.25 mg is commonly employed in adults with normal renal function. In the elderly and in those with renal impairment, a reduced dose of 0.125 or 0.0625 mg o.d. should be used.
- The digoxin concentration should be checked early during chronic therapy in those with normal renal function. Steady

state may take longer to be achieved in those with renal impairment.
- There is no evidence that regular digoxin concentration measurements confer better outcomes. The therapeutic serum concentration should be between 0.6 and 1.2 ng/mL, lower than previously recommended.
- Certain drugs may increase plasma digoxin levels (amiodarone, diltiazem, verapamil, certain antibiotics, quinidine).

Potential adverse effects

- Sinoatrial and AV block
- Atrial and ventricular arrhythmias, especially in the presence of hypokalaemia (digoxin-specific Fab antibody fragments should be considered for ventricular arrhythmias caused by toxicity)
- Signs of toxicity include: confusion, nausea, anorexia, and disturbance of colour vision.

Diuretics (*Table 21*)

Diuretics are recommended in patients with HF and clinical signs or symptoms of congestion.

Class of recommendation I, level of evidence B

Key points

- Diuretics provide relief from the symptoms and signs of pulmonary and systemic venous congestion in patients with HF.[123]
- Diuretics cause activation of the renin–angiotensin–aldosterone system in patients with mild symptoms of HF and should usually be used in combination with an ACEI/ARB.
- The dose requirement must be tailored to the individual patient's needs and requires careful clinical monitoring.
- In general, a loop diuretic will be required in moderate or severe HF.
- A thiazide may be used in combination with loop diuretics for resistant oedema, but with caution to avoid dehydration, hypovolaemia, hyponatraemia, or hypokalaemia.
- It is essential to monitor potassium, sodium, and creatinine levels during diuretic therapy.

Diuretics and ACEIs/ARBs/aldosterone antagonists

- Volume depletion and hyponatraemia from excessive diuresis may increase the risk of hypotension and renal dysfunction with ACEI/ARB therapy.
- If an ACEI/ARB/aldosterone antagonist is used with a diuretic, potassium replacement will usually not be required.
- Serious hyperkalaemia can occur if potassium-sparing diuretics, including aldosterone antagonists, are used in combination with ACEIs/ARBs. Non-aldosterone antagonist potassium-sparing diuretics should be avoided. The combination of an aldosterone antagonist and an ACEI/ARB should only be used under careful supervision.

Table 21 Practical considerations in treatment of heart failure with loop diuretics

Problems	Suggested action
Hypokalaemia/hypomagnesaemia	• Increase ACEI/ARB dosage • Add aldosterone antagonist • Potassium supplements • Magnesium supplements
Hyponatraemia	▪ Fluid restriction • Stop thiazide diuretic or switch to loop diuretic, if possible • Reduce dose/stop loop diuretics if possible • Consider AVP antagonist, e.g. tolvaptan if available • i.v. Inotropic support • Consider ultrafiltration
Hyperuricaemia/gout	▪ Consider allopurinol • For symptomatic gout use colchicine for pain relief • Avoid NSAIDs
Hypovolaemia/dehydration	▪ Assess volume status • Consider diuretic dosage reduction
Insufficient response or diuretic resistance	▪ Check compliance and fluid intake • Increase dose of diuretic • Consider switching from furosemide to bumetanide or torasemide • Add aldosterone antagonist • Combine loop diuretic and thiazide/metolazone • Administer loop diuretic twice daily or on empty stomach • Consider short-term i.v. infusion of loop diuretic
Renal failure (excessive rise in urea/BUN and/or creatinine)	▪ Check for hypovolaemia/dehydration • Exclude use of other nephrotoxic agents, e.g. NSAIDs, trimethoprim • Withhold aldosterone antagonist • If using concomitant loop and thiazide diuretic stop thiazide diuretic • Consider reducing dose of ACEI/ARB • Consider ultrafiltration

How to use diuretics in heart failure

Initiation of diuretic therapy

- Check renal function and serum electrolytes.
- Most patients are prescribed loop diuretics rather than thiazides due to the higher efficiency of induced diuresis and natriuresis.

Diuretic dosages (*Table 22*)

- Start with a low dosage and increase until clinical improvement of the symptoms and signs of congestion.
- Dose must be adjusted, particularly after restoration of dry body weight, to avoid the risk of renal dysfunction and dehydration. Aim to maintain 'dry weight' with lowest achievable dose.
- Self-adjustment of diuretic dose based on daily weight measurements and other clinical signs of fluid retention should be encouraged in HF outpatient care. Patient education is required.
- Management of diuretic resistance is presented in *Table 21*.

Other drugs used to treat cardiovascular co-morbidity in patients with heart failure

Anticoagulants (vitamin K antagonists)

Warfarin (or an alternative oral anticoagulant) is recommended in patients with HF and permanent, persistent, or paroxysmal AF without contraindications to anticoagulation. Adjusted-dose anticoagulation reduces the risk of thromboembolic complications including stroke.

Class of recommendation I, level of evidence A

Anticoagulation is also recommended in patients with intracardiac thrombus detected by imaging or evidence of systemic embolism.

Class of recommendation I, level of evidence C

Key evidence

- The evidence that anticoagulants are effective in reducing thromboembolism in patients with AF is summarized in the joint ACC/AHA/ESC guidelines.[124]
- In a series of randomized trials in patients with AF, which included patients with HF, warfarin reduced the risk of stroke by 60–70%.
- Warfarin was more effective in reducing the risk of stroke than antiplatelet therapy and is preferred over antiplatelet therapy in patients at high risk of stroke, such as those with HF.[125]
- There is no proven role for anticoagulation in other patients with HF, except in those with a prosthetic valve.

Antiplatelet agents

Key evidence

- Antiplatelet agents are not as effective as warfarin in reducing the risk of thromboembolism in patients with AF.
- In a pooled analysis of two small trials comparing warfarin and aspirin in patients with HF, the risk of HF hospitalization was significantly greater in aspirin-treated, compared with warfarin-treated, patients.[126]
- There is no evidence that antiplatelet agents reduce atherosclerotic risk in patients with HF.

HMG CoA reductase inhibitors ('statins')

In elderly patients with symptomatic chronic HF and systolic dysfunction caused by CAD, statin treatment may be considered to reduce cardiovascular hospitalization.

Table 22 Diuretic dosages in patients with heart failure

Diuretics	Initial dose (mg)		Usual daily dose (mg)	
Loop diuretics*				
• Furosemide	20–40		40–240	
• Bumetanide	0.5–1.0		1–5	
• Torasemide	5–10		10–20	
Thiazides**				
• Bendroflumethiazide	2.5		2.5–10	
• Hydrochlorothiazide	25		12.5–100	
• Metolazone	2.5		2.5–10	
• Indapamide†	2.5		2.5–5	
Potassium-sparing diuretics***				
	+ACEI/ARB	−ACEI/ARB	+ACEI/ARB	−ACEI/ARB
• Spironolactone/eplerenone	12.5–25	50	50	100–200
• Amiloride	2.5	5	20	40
• Triamterene	25	50	100	200

*Dose might need to be adjusted according to volume status/weight; excessive doses may cause renal impairment and ototoxicity.
**Do not use thiazides if eGFR <30 mL/min, except when prescribed synergistically with loop diuretics.
***Aldosterone antagonists should always be preferred to other potassium-sparing diuretics.
†Indapamide is a non-thiazide sulphonamide.

Class of recommendation IIb, level of evidence B

Key evidence

- Most trials with statins excluded patients with HF. Only one trial, CORONA, specifically studied a statin in patients with symptomatic HF, ischaemic aetiology, and reduced EF. Rosuvastatin did not reduce the primary end-point (cardiovascular death, MI, or stroke) or all-cause mortality. The number of hospitalizations for cardiovascular causes was reduced significantly.[127]
- The value of statins in HF patients with a non-ischaemic aetiology is unknown.

Management of patients with heart failure and preserved left ventricular ejection fraction (HFPEF)

- No treatment has yet been shown, convincingly, to reduce morbidity and mortality in patients with HFPEF. Diuretics are used to control sodium and water retention and relieve breathlessness and oedema. Adequate treatment of hypertension and myocardial ischaemia is also considered to be important, as is control of the ventricular rate in patients with AF. Two very small studies (<30 patients each) have shown that the heart rate-limiting calcium channel blocker verapamil may improve exercise capacity and symptoms in these patients.[128,129]
- The 3023 patient Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM)-Preserved trial did not show a significant reduction in the risk of the primary composite end-point (adjudicated death from cardiovascular causes or admission with HF) but did show a significant reduction in the risk of investigator-reported admissions for HF.[130] The 850 patient Perindopril for Elderly People with Chronic Heart failure (PEP-CHF) study failed to show a reduction in this composite primary end-point over the total duration of the trial, but showed a significant reduction in cardiovascular death and HF hospitalization at 1 year.[131]

Devices and surgery

Revascularization procedures, valvular and ventricular surgery

- If clinical symptoms of HF are present, surgically correctable conditions should be detected and corrected if indicated.
- CAD is the most common cause of HF and is present in 60–70% of patients with HF and impaired LVEF.[132,133] In HFPEF, CAD is less frequent but still may be detected in up to half of these patients.[39] Ischaemic aetiology is associated with a higher risk of mortality and morbidity.

Revascularization in patients with heart failure

Both a coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) should be considered in selected HF patients with CAD. Decisions regarding the choice of the method of revascularization should be based on a careful evaluation of co-morbidities, procedural risk, coronary anatomy and evidence of the extent of viable myocardium in the area to be revascularized, LV function, and the presence of haemodynamically significant valvular disease.

Key evidence

There are no data from multicentre trials assessing the value of revascularization procedures for the relief of HF symptoms. However, single-centre, observational studies on HF of ischaemic origin suggest that revascularization may lead to symptomatic improvement and potentially improve cardiac function. Clinical trials are ongoing that address the effect of intervention on clinical outcomes.[134]

Evaluation for coronary artery disease in heart failure patients with unknown coronary artery status

Routine coronary angiography is not recommended.

In patients at low risk for CAD: the results of non-invasive evaluation should determine the indication for subsequent angiography (exercise ECG, stress echocardiography, stress nuclear perfusion imaging).

Coronary angiography

- is recommended in patients at high risk for CAD without contraindications to establish diagnosis and plan treatment strategy.

Class of recommendation I, level of evidence C

- is recommended in patients with HF and evidence of significant valvular disease.

Class of recommendation I, level of evidence C

- should be considered in patients with HF who experience anginal symptoms despite optimal medical therapy

Class of recommendation IIa, level of evidence C

Detection of viable myocardium

As viable myocardium may be a target for revascularization, its detection should be considered in the diagnostic work-up in HF patients with CAD. Several imaging modalities with comparable diagnostic accuracy may be employed to detect dysfunctional but viable myocardium (dobutamine echocardiography, nuclear imaging by SPECT and/or by PET, MRI with dobutamine and/or with contrast agents, CT with contrast agents).[135]

Class of recommendation IIa, level of evidence C

Valvular surgery

- Valvular heart disease (VHD) may be the underlying aetiology for HF or an important aggravating factor that requires specific management.
- The ESC Guidelines on the management of valvular disease apply to most patients with HF.[136] Although impaired LVEF is

an important risk factor for higher peri- and postoperative mortality, surgery may be considered in symptomatic patients with poor LV function.
- Optimal medical management of both HF and co-morbid conditions prior to surgery is imperative. Emergency surgery should be avoided if possible.
- Specific recommendations concerning surgery for patients with VHD and HF are difficult to provide. Decisions should be based on a thorough clinical and echocardiographic assessment with attention to cardiovascular and non-cardiovascular co-morbidities. Decisions concerning surgery for haemodynamically important aortic stenosis, aortic regurgitation, or mitral regurgitation require careful consideration of the patient's motivation, biological age and risk profile.

Aortic valve surgery

Aortic stenosis (AS)

Medical treatment should be optimized but not delay the decision regarding valve surgery. Vasodilators (ACEIs, ARBs, and nitrates) may cause substantial hypotension in patients with severe AS and should be used only with great caution.

Surgery

- is recommended in eligible patients with HF symptoms and severe AS.

Class of recommendation I, level of evidence C

- is recommended in asymptomatic patients with severe AS and impaired LVEF (<50%).

Class of recommendation I, level of evidence C

- may be considered in patients with a severely reduced valve area and LV dysfunction.

Class of recommendation IIb, level of evidence C

Aortic regurgitation (AR)

Surgery

- is recommended in all eligible patients with severe AR who have symptoms of HF.

Class of recommendation I, level of evidence B

- is recommended in asymptomatic patients with severe AR and moderately impaired LVEF (LVEF ≤50%).

Class of recommendation IIa, level of evidence C

Key evidence

LV function usually improves after surgery, and one non-randomized study showed improved survival compared with controls.[137] On the other hand, risk of surgery is highest in patients with most advanced LV dysfunction.[136]

Mitral valve surgery

Mitral regurgitation (MR)

Surgery

- In patients with HF and severe mitral valve regurgitation, symptomatic improvement has been reported in selected patients. Surgery should be considered in patients with severe MR whenever coronary revascularization is an option. Surgical repair of the valve may represent an attractive option in carefully selected patients.[136]

Organic mitral regurgitation

- In patients with severe organic MR due to a structural abnormality or damage to the mitral valve, development of HF symptoms is a strong indication for surgery.

Surgery

- is recommended for patients with LVEF >30% (valve repair if possible).

Class of recommendation I, level of evidence C

- may be considered for patients with severe MR and LVEF <30%; medical therapy should be a first choice. Only if patients remain refractory to pharmacological treatment and have a low risk profile should surgery be considered.

Class of recommendation IIb, level of evidence C

Functional mitral regurgitation

Surgery

- may be considered in selected patients with severe functional MR and severely depressed LV function, who remain symptomatic despite optimal medical therapy.

Class of recommendation IIb, level of evidence C

- Cardiac resynchronization therapy (CRT) should be considered in eligible patients as it may improve LV geometry, papillary muscle dyssynchrony and may reduce MR (see section Devices and surgery).

Class of recommendation IIa, level of evidence B

Ischaemic mitral regurgitation

Surgery

- is recommended in patients with severe MR and LVEF >30% when CABG is planned.

Class of recommendation I, level of evidence C

- should be considered in patients with moderate MR undergoing CABG if repair if feasible.

Class of recommendation IIa, level of evidence C

Tricuspid regurgitation (TR)

- Functional TR is extremely common in HF patients with biventricular dilatation, systolic dysfunction, and pulmonary

hypertension. Symptoms of right-sided HF with systemic congestion respond poorly to aggressive diuretic therapy, which may aggravate symptoms such as fatigue and exercise intolerance. Surgery for isolated functional TR is not indicated.

Class of recommendation III, level of evidence C

Left ventricular aneurysmectomy

- LV aneurysmectomy may be considered in symptomatic patients with large, discrete LV aneurysms.

Class of recommendation IIb, level of evidence C

Cardiomyoplasty

- Cardiomyoplasty and partial left ventriculectomy (Batista operation) is not recommended for the treatment of HF or as an alternative to heart transplantation.

Class of recommendation III, level of evidence C

External ventricular restoration

- External ventricular restoration is not recommended for the treatment of HF.

Class of recommendation III, level of evidence C

Pacemakers

- The conventional indications for patients with normal LV function also apply to patients with HF. In patients with HF and sinus rhythm, maintenance of a normal chronotropic response and coordination of atrial and ventricular contraction with a DDD pacemaker may be especially important.[138]
- In HF patients with concomitant indication for permanent pacing (first implant or upgrading of a conventional pacemaker) and NYHA class II–IV symptoms, low LVEF ≤35%, or LV dilatation, CRT with pacemaker function (CRT-P) should be considered. In these patients, the use of right ventricular pacing may be deleterious and may cause or increase dyssynchrony.[138]

Class of recommendation IIa, level of evidence C

Cardiac resynchronization therapy (CRT) (*Table 23*)

- CRT-P is recommended to reduce morbidity and mortality in patients in NYHA III–IV class who are symptomatic despite optimal medical therapy, and who have a reduced EF (LVEF ≤35%) and QRS prolongation (QRS width ≥120 ms).

Class of recommendation I, level of evidence A

- CRT with defibrillator function (CRT-D) is recommended to reduce morbidity and mortality in patients in NYHA III–IV class who are symptomatic despite optimal medical therapy, and who have a reduced EF (LVEF ≤35%) and QRS prolongation (QRS width ≥120 ms)

Table 23 Class I recommendations for devices in patients with LV systolic dysfunction

ICD	
Prior resuscitated cardiac arrest	Class I Level A
Ischaemic aetiology and >40 days of MI	Class I Level A
Non-ischaemic aetiology	Class I Level B
CRT	
NYHA Class III/IV and QRS >120 ms	Class I Level A
To improve symptoms/reduce hospitalization	Class I Level A
To reduce mortality	Class I Level A

Class of recommendation I, level of evidence A

- The survival advantage of CRT-D vs. CRT-P has not been adequately addressed. Due to the documented effectiveness of ICD therapy in the prevention of sudden cardiac death, the use of a CRT-D device is commonly preferred in clinical practice in patients satisfying CRT criteria including an expectation of survival with good functional status for >1 year.

Key evidence

- CRT is used in order to synchronize interventricular and intraventricular contraction in patients with HF in whom there is evidence of electrical dyssynchrony (QRS width ≥120 ms). Several single-centre observational studies have suggested that one or more measures of mechanical dyssynchrony may predict benefit with CRT in patient selection. Although CRT devices have been implanted in patients without ECG evidence of electrical dyssynchrony (QRS width <120 ms) based on echocardiographic evidence of dyssynchrony, there is no trial evidence supporting this practice.[139] The recently published PROSPECT trial does not support the use of echocharidiographic and tissue Doppler-based indices of mechanical synchrony in the selection of patients.[140]
- The first clinical trials investigating the value of CRT in the management of patients with NYHA class III and IV HF, a reduced LVEF, and a wide QRS demonstrated that CRT improves functional class, exercise duration, and quality of life.[141–145]
- Two major trials investigated the effect of CRT on all-cause mortality in HF patients with class III and IV HF and dyssynchrony. In COMPANION,[142] CRT-P and CRT-D were both associated with a 20% reduction in the primary combined end-point of all-cause mortality and all-cause hospitalization ($P < 0.01$). CRT-D was associated with a significant decrease in total mortality ($P = 0.003$), whereas reduction in mortality associated with CRT-P was not statistically significant ($P = 0.059$). It is important to note that the study was not designed or powered to evaluate effects on total mortality nor to compare CRT-P and CRT-D, and conclusive data comparing the effect of CRT-P to CRT-D are not available.
- In the CARE-HF trial,[143] CRT-P was associated with a significant reduction of 37% in the composite end-point of total death and hospitalization for major cardiovascular events ($P < 0.001$) and

of 36% in total mortality ($P < 0.002$). A recent meta-analysis showed that the reduction in all-cause mortality was 29%.[144] It should be noted that the meta-analysis failed to demonstrate that CRT-D improved survival when compared with implantable defibrillator therapy (0.82, 0.57–1.18) or resynchronization alone (CRT-P) (0.85, 0.60–1.22).

- Natriuretic peptide levels are powerful markers of increased cardiovascular risk, CRT reduces NT-proBNP substantially, and reduction in NT-proBNP is associated with a better outcome.[145] Patients with marked elevation of NT-proBNP receive a smaller relative benefit from CRT but, due to their higher risk, the absolute benefit is similar.

Implantable cardioverter defibrillator (ICD) (*Table 23*)

- ICD therapy for *secondary prevention* is recommended for survivors of ventricullar fibrillation (VF) and also for patients with documented haemodynamically unstable VT and/or VT with syncope, a LVEF ≤40%, on optimal medical therapy, and with an expectation of survival with good functional status for >1 year.

Class of recommendation I, level of evidence A

- ICD therapy *for primary prevention* is recommended to reduce mortality in patients with LV dysfunction due to prior MI who are at least 40 days post-MI, have an LVEF ≤35%, in NYHA functional class II or III, receiving optimal medical therapy, and who have a reasonable expectation of survival with good functional status for >1 year.

Class of recommendation I, level of evidence A

- ICD therapy for *primary* prevention is recommended to reduce mortality in patients with non-ischaemic cardiomyopathy with an LVEF ≤35%, in NYHA functional class II or III, receiving optimal medical therapy, and who have a reasonable expectation of survival with good functional status for >1 year.

Class of recommendation I, level of evidence B

Key evidence

- Approximately half of the deaths observed in patients with HF are related to sudden cardiac death (SCD). Reduction of the proportion of patients dying for an arrhythmic event is therefore an important part of the effort to reduce total mortality in this population.
- **Treatment of the arrhythmogenic substrate in HF**
  Pharmacological intervention in patients with HF has been confirmed to reduce morbidity and mortality substantially. A reduction of sudden cardiac death should be considered an important indication in planning a treatment strategy in patients with HF.
- **Secondary prevention of cardiac arrest**
  Clinical trials in post-MI patients who have survived a cardiac arrest have demonstrated that the use of an ICD is more effective than antiarrhythmic drugs in the prevention of SCD.[146–148] Meta-analyses of primary prevention trials have shown that the benefit on survival with ICDs is highest in the post-MI patients with depressed systolic function (LVEF ≤35%).[149] No studies have addressed the population with a non-ischaemic aetiology who survived a cardiac arrest.
- **Primary prevention of cardiac arrest**
  The results of drug trials performed in the 1980s[150] and 1990s[151–156] with class I and III antiarrhythmic drugs did not demonstrate efficacy. The SCD-HeFT[157] trial demonstrated a lack of survival benefit in patients in NYHA functional class II and III and with an LVEF ≤35% treated with amiodarone, irrespective of the aetiology of HF.

  Most of the ICD trials for primary prevention of SCD have focused on patients with HF of ischaemic aetiology,[158–162] and have included patients with a reduced EF. Unfortunately the different trials have used variable cut-offs of EF (≤30%, ≤35%, or ≤40%). This heterogeneity accounts for the slightly different recommendations produced by various guideline task forces.[163] Importantly, there is discrepancy between the protocol inclusion EF criteria for the randomized trials and the actual average EF of the study cohorts. The strongest evidence exists for patients in NYHA classes II and III. The data for patients in NYHA class I are less robust.

  Data on the role of the ICD in patients with non-ischaemic dilated cardiomyopathy (DCM) are more limited.[164–166] The SCD-HeFT trial[157] enrolled patients with both DCM and ischaemic LV dysfunction, and showed a 23% reduction in mortality. A meta-analysis of trials enrolling only non-ischaemic DCM patients showed a 25% reduction in mortality in the group of patients receiving an ICD ($P = 0.003$).[167] These data suggest that the aetiology of HF may not justify a different approach for the primary prevention of SCD. A useful algorithm for selecting patients for device therapy (CRT, ICD) is presented in *Figure 2*.

Heart transplantation, ventricular assist devices, and artificial hearts

Heart transplantation

Heart transplantation is an accepted treatment for end-stage HF. Although controlled trials have never been conducted, there is consensus that transplantation, provided proper selection criteria are applied, significantly increases survival, exercise capacity, return to work, and quality of life compared with conventional treatment.

Class of recommendation I, level of evidence C

Key points

Patients with severe HF symptoms, a poor prognosis, and with no alternative form of treatment should be considered for heart transplantation. The introduction of new techniques and more sophisticated pharmacological treatment has modified the prognostic significance of the variables traditionally used to identify heart transplant candidates (peak VO_2). The patient must be well informed, motivated, emotionally stable, and capable of complying with intensive medical treatment.

Apart from the shortage of donor hearts, the main challenge of heart transplantation is prevention of 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 long-term immunosuppression therapy (infection, hypertension, renal failure, malignancy, and CAD). Heart transplantation should be considered in motivated patients with end-stage HF, severe symptoms, no serious co-morbidity, and no alternative treatment options. The contraindications include: current alcohol and/or drug abuse, lack of proper cooperation, serious mental disease not properly controlled, treated cancer with remission and <5 years follow-up, systemic disease with multiorgan involvement, active infection, significant renal failure (creatinine clearance <50 mL/min), irreversible high pulmonary vascular resistance (6–8 Wood units and mean transpulmonary gradient >15 mmHg), recent thromboembolic complications, unhealed peptic ulcer, evidence of significant liver impairment, or other serious co-morbidity with a poor prognosis.

Left ventricular assist devices (LVAD) and artificial hearts

There has been rapid progress in the development of LVAD technology and artificial hearts. Due to the nature of the target population, there is limited documentation from randomized clinical trials. The current recommendations reflect this limited evidence. There is therefore no consensus concerning LVAD indications or the most appropriate patient population. LVAD technology is likely to undergo substantial improvement in the near future, and the recommendations will need revision accordingly.[168,169]

- Current indications for LVADs and artificial hearts include bridging to transplantation and managing patients with acute, severe myocarditis.

Class of recommendation IIa, level of evidence C

- Although experience is limited, these devices may be considered for long-term use when no definitive procedure is planned.

Class of recommendation IIb, level of evidence C

Key evidence

Haemodynamic support with an LVAD may prevent or reduce clinical deterioration and may improve the patient's clinical condition prior to transplant, or reduce mortality in patients with severe acute myocarditis. During longer term support, the risk of complications, including infection and embolization, increases.

Ultrafiltration

Ultrafiltration should be considered to reduce fluid overload (pulmonary and/or peripheral oedema) in selected patients and correct hyponatraemia in symptomatic patients refractory to diuretics.

Class of recommendation IIa, level of evidence B

Key evidence

Although earlier studies suggested only temporary benefit, more recent trials have demonstrated sustained effects.[170] The most appropriate selection criteria have not been established. However, technological advances facilitate ultrafiltration and will probably increase experience in this population.

Remote monitoring

Remote monitoring can be summarized as the continuous collection of patient information and the capability to review this information without the patient present. The collection of this information may require patient participation for measures such as weight, BP, ECG, or symptoms. Newer implanted devices provide access to information such as heart rate, arrhythmia episodes, activity, intracardiac pressure, or thoracic impedance without the need to actively involve the patient.

Continuous analysis of these trends can activate notification mechanisms when clinically relevant changes are detected, and therefore facilitate patient management. Although unproven, remote monitoring may decrease healthcare utilization through fewer hospital admissions for chronic HF, fewer heart failure-related re-admissions, and more efficient device management. Ongoing trials will assess the clinical utility of such an approach.

Class of recommendation IIb, level of evidence C

Arrhythmias in heart failure

The ACC/AHA/ESC Guidelines for management of patients with arrhythmias[124] are applicable to patients with HF. This section emphasizes aspects of management that are particularly relevant in HF.

Atrial fibrillation (*Table 24*)

AF is the most common arrhythmia in HF. Its onset may lead to worsening of symptoms, an increased risk of thromboembolic complications, and poorer long-term outcomes. AF

Table 24 Management of patients with heart failure and atrial fibrillation

General recommendations
• Precipitating factors and co-morbidities should be identified
• HF treatment should be optimized
Rhythm control
• Immediate electrical cardioversion is recommended for patients with new-onset AF and myocardial ischaemia, symptomatic hypotension or symptoms of pulmonary congestion or rapid ventricular response not controlled by appropriate pharmacological measures
Rate control
• Digoxin alone or in combination with β-blocker is recommended
Prevention of thromboembolism
• Antithrombotic therapy is recommended, unless contraindicated
• Optimal approach should be based on risk stratification: in patients at highest risk of stroke [prior stroke, transient ischaemic attack (TIA), or systemic embolism] oral anticoagulant therapy with a vitamin K antagonist is recommended

may be classified as: first episode, paroxysmal, persistent, or permanent.

- Potential precipitating factors and co-morbidity should be identified and, if possible, corrected (e.g. electrolyte abnormalities, hyperthyroidism, alcohol consumption, mitral valve disease, acute ischaemia, cardiac surgery, acute pulmonary disease, infection, uncontrolled hypertension).
- Background HF treatment should be carefully re-evaluated and optimized.
- Management of HF patient with AF, involves three objectives: rate control; correction of the rhythm disturbance; and prevention of thromboembolism.[171]
- Most patients with symptomatic HF are treated with a β-blocker, and caution is advised when adding an anti-arrhythmic agent.

The following recommendations are particularly applicable for HF patients:

Pharmacological rate control during atrial fibrillation (see section Pharmacological therapy)

- A β-blocker or digoxin is recommended to control the heart rate at rest in patients with HF and LV dysfunction.

Class of recommendation I, level of evidence B

- A combination of digoxin and a β-blocker may be considered to control the heart rate at rest and during exercise.
- In LV systolic dysfunction, digoxin is the recommended initial treatment in haemodynamically unstable patients.
- Intravenous administration of digoxin or amiodarone is recommended to control the heart rate in patients with AF and HF, who do not have an accessory pathway.

Class of recommendation I, level of evidence B

- In patients with HF and preserved LVEF, a non-dihydropyridine calcium channel antagonist (alone or in combination with digoxin) should be considered to control the heart rate at rest and during exercise.

Class of recommendation IIa, level of evidence C

- Atrioventricular node ablation and pacing should be considered to control the heart rate when other measures are unsuccessful or contraindicated.

Class of recommendation IIa, level of evidence B

Prevention of thromboembolism (see section Pharmacological therapy)

- Antithrombotic therapy to prevent thromboembolism is recommended for all patients with AF, unless contraindicated.

Class of recommendation I, level of evidence A

- In patients with AF at highest risk of stroke such as prior thromboembolism, stroke, transient ischaemic attack, or systemic embolism, chronic oral anticoagulant therapy with a vitamin K antagonist to achieve the target international normalized ratio (INR) of 2.0–3.0 is recommended, unless contraindicated

Class of recommendation I, level of evidence A

- Anticoagulation is recommended for patients with >1 moderate risk factor. Such factors include: age ≥75 years, hypertension, HF, impaired LV function (LVEF ≤35%), and diabetes mellitus.

Class of recommendation I, level of evidence A

- In patients with HF and AF who do not have any additional risk factors (see above), therapy with either aspirin (81–325 mg daily) or a vitamin K antagonist is reasonable for primary prevention of thromboembolism.

Class of recommendation IIa, level of evidence A

Rhythm control

There is no clear evidence that restoring and maintaining sinus rhythm is superior to rate control in reducing morbidity and mortality in patients with persistent AF and HF.[172]

- Electrical cardioversion is recommended when the rapid ventricular rate does not respond promptly to appropriate pharmacological measures and especially in patients with AF causing myocardial ischaemia, symptomatic hypotension, or symptoms of pulmonary congestion. Precipitating factors should be detected and treated. TOE may be required to rule out atrial thrombus.

Class of recommendation I, level of evidence C

- In patients who require immediate cardioversion because of haemodynamic instability, the following approach to prevent thromboembolism is recommended:

  If AF is of ≥48 h duration or of unknown duration, heparin by i.v. bolus should be administered followed by a continuous infusion. Subcutaneous, low molecular weight heparin is an acceptable alternative. TOE may be required.

Class of recommendation I, level of evidence C

- In patients with AF and HF and/ or depressed LV function, the use of antiarrhythmic therapy to maintain sinus rhythm should be restricted to amiodarone.

Class of recommendation I, level of evidence C

- In patients with symptomatic HF and persistent (non-self-terminating) AF, electrical cardioversion should be considered, although its success rate may depend on the duration of arrhythmia and left atrial size.

Class of recommendation IIa, level of evidence C

- Administration of i.v. amiodarone is a reasonable option for pharmacological cardioversion of AF, particularly when rapid restoration of sinus rhythm is not required. Patients should be anticoagulated.

Class of recommendation IIa, level of evidence A

- Invasive, catheter-based ablation procedures (pulmonary vein isolation) should be considered in refractory patients but have not been evaluated in clinical trials.

Class of recommendation IIa, level of evidence C

Ventricular arrhythmias

Ventricular arrhythmias (VAs) are frequent in HF patients, particularly in those with a dilated LV and reduced LVEF. Ambulatory ECG recordings detect premature ventricular complexes in virtually all HF patients, and episodes of asymptomatic, non-sustained VT are common. Complex VA is associated with a poor outcome.

On the basis of existing evidence including recent ACC/AHA/ESC Guidelines for management of VAs and sudden death,[163] the following recommendations are particularly applicable for HF patients with VA:

- It is essential to detect and, if possible, correct all potential factors precipitating VA. Neurohumoral blockade with optimal doses of β-blockers, ACEIs, ARBs, and/or aldosterone blockers is recommended.

Class of recommendation I, level of evidence A

- VA may be caused by myocardial ischaemia in HF, and aggressive therapy is essential. Evaluation for CAD and the potential for revascularization is recommended in high-risk patients.

Class of recommendation I, level of evidence C

- Routine, prophylactic use of antiarrhythmic agents in patients with asymptomatic, non-sustained VA is not recommended. In HF patients, class Ic agents should not be used.

Class of recommendation III, level of evidence B

Patients with heart failure and symptomatic VA (see section Devices and Surgery)

- In patients who survived VF or had a history of haemodynamically unstable VT or VT with syncope, with reduced LVEF (<40%), receiving optimal pharmacological treatment and with a life expectancy of >1 year, ICD implantation is recommended.

Class of recommendation I, level of evidence A

- Amiodarone is recommended in patients with an implanted ICD, otherwise optimally treated, who continue to have symptomatic VA.

Class of recommendation I, level of evidence C

- Catheter ablation is recommended as a adjunct therapy in patients with an ICD implanted who have recurrent symptomatic VT with frequent shocks that is not curable by device reprogramming and drug therapy.[173]

Class of recommendation I, level of evidence C

- Amiodarone may be considered as an alternative to ICD to suppress symptomatic VT in already optimally treated HF patients in whom ICD is not an alternative.

Class of recommendation IIb, level of evidence C

- Amiodarone may be considered in HF patients with ICD implanted who have recurrent symptomatic VT with frequent ICD shocks despite optimal therapy to prevent discharge.

Class of recommendation IIb, level of evidence C

- Electrophysiological evaluation and catheter ablation techniques may be considered in patients with HF and serious VA refractory to management.

Class of recommendation IIb, level of evidence C

Bradycardia

The indications for pacing in patients with HF are similar to those of other patients. These recommendations are detailed in the ESC Guidelines on pacing[138] and further discussed in the Devices and surgery section of these guidelines. Several points specifically related to patients with HF deserve mention.

- Physiological pacing to maintain an adequate chronotropic response and maintain atrial–ventricular coordination with a DDD system is preferable to VVI pacing in patients with HF.
- The indications for an ICD, CRT-P, or CRT-D device should be detected and evaluated in patients with HF prior to implantation of a pacemaker for an AV conduction defect.
- Right ventricular pacing may induce dyssynchrony and worsen symptoms.[174]
- Pacing in order to permit initiation or titration of β-blocker therapy in the absence of conventional indications is not recommended.

Co-morbidities and special populations

Hypertension, CAD, and valvular dysfunction are frequently causal risk factors for HF or may co-exist with another primary aetiology. It is useful to highlight aspects of these conditions that may influence diagnosis, treatment, and prognosis in patients with HF (See section Devices and surgery).

Arterial hypertension (*Table 25*)

- Treatment of hypertension substantially reduces the risk of developing HF. Optimal values have not been established, but according to the current ESH/ESC Guidelines[175] target BP: (i) should be reduced to at least below 140/90 mmHg (systolic/diastolic), and to lower values if tolerated, in all hypertensive

Table 25 Management of arterial hypertension in patients with heart failure

In hypertensive patients with evidence of LV dysfunction
• Systolic and diastolic blood pressure should be carefully controlled with a therapeutic target of ≤140/90 and ≤130/80 mmHg in diabetics and high risk patients
• Anti-hypertensive regimens based on renin–angiotensin system antagonists (ACEIs or ARBs) are preferable
In hypertensive patients with HFPEF:
• Aggressive treatment (often with several drugs with complementary mechanisms of action) is recommended
• ACEIs and/or ARBs should be considered the first-line agents

patients; and (ii) should be <130/80 mmHg in diabetics and other high risk patients, such as those with evidence of target organ damage (stroke, MI, renal dysfunction, proteinuria).

Class of recommendation I, level of evidence A

Diabetes mellitus (DM)

Key points

- DM is a major risk factor for the development of cardiovascular disease and HF.[176,177]
- ACEIs and ARBs can be useful in patients with DM to decrease the risk of end-organ damage and cardiovascular complications and subsequently risk of HF.

Class of recommendation IIa, level of evidence A for ACEI and C for ARB

- DM is a frequent co-morbidity in HF, affecting 20–30% of patients.[178] DM may have a deleterious impact on the natural course of HF particularly in those with ischaemic cardiomyopathy. DM and ischaemic heart disease may interact to accelerate the deterioration of myocardial dysfunction, HF progression, and unfavourably influence prognosis.[179,180]
- Although the relationship between elevated glucose level and a higher risk for HF is established in patients with DM, a direct beneficial effect of glucose lowering in reducing the risk of HF has not been convincingly demonstrated.[181]

Management of DM in patients with HF

The recommendations in the ESC/EASD Guidelines for the management of DM apply to most patients with HF.[181] In HF the following specific issues are of special interest:

- All patients should receive lifestyle recommendations.

Class of recommendation I, level of evidence A

- Elevated blood glucose should be treated with tight glycaemic control.

Class of recommendation IIa, level of evidence A

- Oral antidiabetic therapy should be individualized.

Class of recommendation I, level of evidence B

- *Metformin* should be considered as a first-line agent in overweight patients with type II DM without significant renal dysfunction (GFR >30 mL/min).

Class of recommendation IIa, level of evidence B

- *Thiazolidinediones* have been associated with increased peripheral oedema and symptomatic HF. The risk of developing oedema with thiazolidinediones is dose related and higher in diabetic patients who are taking concomitant insulin therapy. They are therefore contraindicated in HF patients with NYHA functional class III–IV, but may be considered in patients with NYHA functional class I–II with careful monitoring for fluid retention.

Class of recommendation IIb, level of evidence B

- Early initiation of insulin may be considered if glucose target cannot be achieved.

Class of recommendation IIb, level of evidence C

- Agents with documented effects on morbidity and mortality such as ACEIs, β-blockers, ARBs, and diuretics confer benefit at least comparable with that demonstrated in non-diabetic HF patients.

Class of recommendation I, level of evidence A

- Evaluation of the potential for revascularization may be particularly important in patients with ischaemic cardiomyopathy and DM.

Class of recommendation IIa, level of evidence C

Renal dysfunction

Key points

- Renal dysfunction is common in HF, and the prevalence increases with HF severity, age, a history of hypertension, or DM.
- In HF, renal dysfunction is strongly linked to increased morbidity and mortality.[182]
- The cause of renal dysfunction should always be sought in order to detect potentially reversible causes such as hypotension, dehydration, deterioration in renal function due to ACEIs, ARBs, or other concomitant medications (e.g. NSAIDs), and renal artery stenosis.[7]

Management of heart failure patients with renal dysfunction

Therapy in HF patients with concomitant renal dysfunction is not evidence-based, as these patients are not adequately represented in RCTs in HF (see section Pharmacological therapy). The following specific issues are of interest:

- Therapy with an ACEI or ARB is usually associated with a mild deterioration in renal function as evidenced by some increase in blood urea nitrogen and creatinine levels and a decrease in estimated GFR. These changes are frequently transient and reversible. Patients with pre-existing renal insufficiency or renal artery stenosis are at a higher risk. If renal deterioration continues, other secondary causes such as excessive diuresis, persistent hypotension, other nephrotoxic therapies, or concurrent renovascular disease should be excluded.
- There is no absolute level of creatinine which precludes the use of ACEIs/ARBs. However, if the serum creatinine level is >250 μmol/L (~2.5 mg/dL), specialist supervision is recommended. In patients with a serum creatinine >500 μmol/L (~5 mg/dL), haemofiltration or dialysis may be needed to control fluid retention and treat uraemia.
- Aldosterone antagonists should be used with caution in patients with renal dysfunction as they may cause significant hyperkalaemia.
- HF patients with renal dysfunction often have excessive salt and water retention, which require more intensive diuretic

treatment. In patients with a creatinine clearance <30 mL/min, thiazide diuretics are ineffective and loop diuretics are preferred.
- Renal dysfunction is associated with impaired clearance of many drugs (e.g. digoxin). To avoid toxicity, the maintenance dose of such drugs should be reduced and plasma levels monitored.

Chronic obstructive pulmonary disease (COPD)

Key points

- COPD is a frequent co-morbidity in HF, and the prevalence ranges between 20 and 30%.[183–185] Restrictive and obstructive pulmonary abnormalities are common.
- COPD patients have a markedly elevated risk of HF, and COPD is a strong and independent risk factor for cardiovascular morbidity and mortality.[186] Co-existing COPD further worsens prognosis in HF patients.[187]
- Diagnostic assessment of HF in the presence of COPD is challenging in clinical practice. There is a significant overlap in the signs and symptoms, with a relatively lower sensitivity of diagnostic tests such as chest X-ray, ECG, echocardiography, and spirometry.[184]
- Evaluation of natriuretic peptide (BNP or NT-proBNP) levels may be helpful in this population, but the results are often intermediate. The negative predictive value may be most useful.[184]
- Accurate quantification of the relative contribution of cardiac and ventilatory components to the disability of the patient is difficult but may be the key to optimal management.[184] It is essential to detect and treat pulmonary congestion.
- Agents with documented effects on morbidity and mortality such as ACEIs, β-blockers, and ARBs are recommended in patients with co-existing pulmonary disease.[184]
- The majority of patients with HF and COPD can safely tolerate β-blocker therapy. Initiation at a low dose and gradual up-titration is recommended. Mild deterioration in pulmonary function and symptoms should not lead to prompt discontinuation. If symptoms worsen, a reduction of the dosage or withdrawal may be necessary. Selective β-blockade may be the preferable option.[188–190]
- A history of asthma should be considered a contraindication to the use of any β-blocker. Inhaled β-agonists should be administered as required in patients with COPD.[191]
- Co-existence of COPD and HF may dramatically reduce exercise tolerance.[192] Supervised rehabilitation programmes may be appropriate to improve skeletal muscle function and fatigue.

Anaemia

- The reported prevalence of anaemia in HF ranges widely from 4 to 70% due to a lack of an established, consistent definition of anaemia in HF. The prevalence of anaemia increases with HF severity, advanced age, female gender, renal disease, and other co-morbidities.[193,194]
- Anaemia in patients with HF is frequently associated with a substantially decreased aerobic capacity, a subjective experience of fatigue and reduced functional status, and poor quality of life.[193,194] Anaemia has been consistently shown to be an independent risk factor for hospital admission and mortality. The most important underlying causes include haemodilution, renal dysfunction, malnutrition, chronic inflammation, impaired bone marrow function, iron deficiency, and drug therapy.[192–196]
- Anaemia may aggravate the pathophysiology of HF by adversely affecting myocardial function, activating neurohormonal systems, compromising renal function, and contributing to circulatory failure.[193,194]
- Correction of anaemia has not been established as routine therapy in HF. Simple blood transfusion is not recommended to treat the anaemia of chronic disease in HF. Among potential therapies, the use of erythropoietin-stimulating agents, usually together with iron, to increase red blood cell production represents an unproven option.[197–200]

Cachexia

- Body wasting is a serious complication of HF, which may affect 10–15% of CHF patients during the natural course of the disease. This is a generalized process that encompasses loss in all body compartments, i.e. lean tissue (skeletal muscle), fat tissue (energy reserves), and bone tissue (osteoporosis).[201] Cachexia can be defined as involuntary non-oedematous weight loss of ≥6% of total body weight within the last 6–12 months.[80]
- Pathophysiology of cachexia in the HF syndrome still remains unclear, and poor nutrition, malabsorption, impaired calorie and protein balance, hormone resistance, proinflammatory immune activation, neurohormonal derangements, and depletion in anabolic drive may be operative.[201]
- Cachexia usually coincides with severe symptoms of dyspnoea and weakness with a poor quality of life. Wasting is also related to very poor outcome. The mortality of cachectic HF patients is higher than in most malignant diseases.[202]
- It has not yet been established whether prevention and treatment of cachexia complicating HF should be a treatment goal. Options include hypercaloric feeding, appetite stimulants, exercise training, and anabolic agents (insulin, anabolic steroids).[202]

Gout

- Patients with HF are prone to develop hyperuricaemia as a result of loop diuretic therapy use and renal dysfunction. Hyperuricaemia confers a poor prognosis in HF. In acute gout a short course of colchicine to suppress pain and inflammation may be considered. NSAIDs should be avoided, if possible, in symptomatic patients. Prophylactic therapy with a xanthine oxidase inhibitor (allopurinol) is recommended to prevent recurrence.

Adults with congenital heart disease

- In children, heart failure is most often related to high-output situations due to intracardiac shunting. This is less frequently observed in adults. Complex lesions associated with cyanosis secondary to impaired pulmonary perfusion may make the diagnosis of HF difficult. Therefore, natriuretic peptide measurements should be included regularly in these patients. Eisenmenger patients represent special problems with

associated right ventricular failure and reduced preload of the LV during exercise. Fontan patients are unable to increase pulmonary perfusion. Many of these patients benefit from afterload reduction even before significant HF symptoms are clinically manifest.[203,204]

The elderly

- Most clinical trials have included younger patients with a mean age of ~61 years, and commonly 70% of patients have been male. Half of the patients with HF in the population are >75 years in age, and only in younger age groups do males predominate. HF with a preserved EF is more common in the elderly and in females.
- HF in the elderly is frequently underdiagnosed, as cardinal symptoms of exercise intolerance are often attributed to ageing, co-existing co-morbidities, and poor health status. Common co-morbidities which may have an impact on management, include renal failure, diabetes, stroke, cognitive impairment, and COPD.
- Polypharmacy increases the risk of adverse interactions and side-effects which may reduce compliance. Altered pharmacokinetic and pharmacodynamic properties of drugs must always be considered. Impairment of renal function is a natural consequence of ageing. Therefore, dosages of ACEIs, ARBs, spironolactone, and digoxin may need adjustment.
- For elderly HF patients suffering from cognitive impairment, individually structured multidisciplinary HF programmes may be particularly useful and may improve adherence to therapy and prevent hospitalization.
- Relative contraindications to diagnostic procedures and interventions should be carefully evaluated and weighed against the indications.

Acute heart failure

Definition

Acute heart failure (AHF) is defined as a rapid onset or change in the signs and symptoms of HF, resulting in the need for urgent therapy. AHF may be either new HF or worsening of pre-existing chronic HF. Patients may present as a medical emergency such as acute pulmonary oedema.

The cardiac dysfunction may be related to ischaemia, abnormalities in cardiac rhythm, valvular dysfunction, pericardial disease, increased filling pressures or elevated systemic resistance. These diverse cardiovascular aetiologies and conditions often interact. *Table 26* presents the common causes and precipitating factors of AHF. It is essential that these factors be identified and incorporated into the treatment strategy.

AHF is usually characterized by pulmonary congestion, although in some patients reduced cardiac output and tissue hypoperfusion may dominate the clinical presentation. Multiple cardiovascular and non-cardiovascular morbidities may precipitate AHF.[4] Common examples include (i) increased afterload due to systemic or pulmonary hypertension; (ii) increased preload due to volume overload or fluid retention; or (iii) circulatory failure as in high output states, i.e. infection, anaemia, or thyrotoxicosis. Other conditions that may precipitate AHF include non-adherence with HF medications or medical advice, drugs such as NSAIDs, cyclo-oxygenase (COX) inhibitors, and thiazolidinediones. Severe AHF may also result in multiorgan failure (see *Table 26*).

Table 26 Causes and precipitating factors of acute heart failure

Ischaemic heart disease	**Circulatory failure**
• Acute coronary syndromes	• Septicaemia
• Mechanical complications of acute MI	• Thyrotoxicosis
• Right ventricular infarction	• Anaemia
Valvular	• Shunts
• Valve stenosis	• Tamponade
• Valvular regurgitation	• Pulmonary embolism
• Endocarditis	**Decompensation of pre-existing chronic HF**
• Aortic dissection	• Lack of adherence
Myopathies	• Volume overload
• Postpartum cardiomyopathy	• Infections, especially pneumonia
• Acute myocarditis	• Cerebrovascular insult
Hypertension/arrhythmia	• Surgery
• Hypertension	• Renal dysfunction
• Acute arrhythmia	• Asthma, COPD
	• Drug abuse
	• Alcohol abuse

The symptoms of HF may be aggravated by non-cardiovascular co-morbidities such as obstructive lung disease or co-existing end-organ disease, especially renal dysfunction.

Appropriate initial and long-term therapy is required. If possible, anatomical correction of the underlying pathology, e.g. valve replacement or revascularization, may prevent further episodes of acute decompensation and improve long-term prognosis.

Clinical classification

The clinical presentation of AHF reflects a spectrum of conditions, and any classification will have its limitations. The patient with AHF will usually present in one of six clinical categories. Pulmonary oedema may or may not complicate the clinical presentation.[4] *Figure 3* demonstrates the potential overlap between these conditions.[205]

- **Worsening or decompensated chronic HF** (peripheral oedema/congestion): there is usually a history of progressive worsening of known chronic HF on treatment, and evidence of systemic and pulmonary congestion. Low BP on admission is associated with a poor prognosis.
- **Pulmonary oedema**: patients present with severe respiratory distress, tachypnoea, and orthopnoea with rales over the lung fields. Arterial O_2 saturation is usually <90% on room air prior to treatment with oxygen.
- **Hypertensive HF**: signs and symptoms of HF accompanied by high BP and usually relatively preserved LV systolic function. There is evidence of increased sympathetic tone with tachycardia and vasoconstriction. The patients may be euvolaemic or only mildly hypervolaemic, and present frequently with signs of pulmonary congestion without signs of systemic congestion.

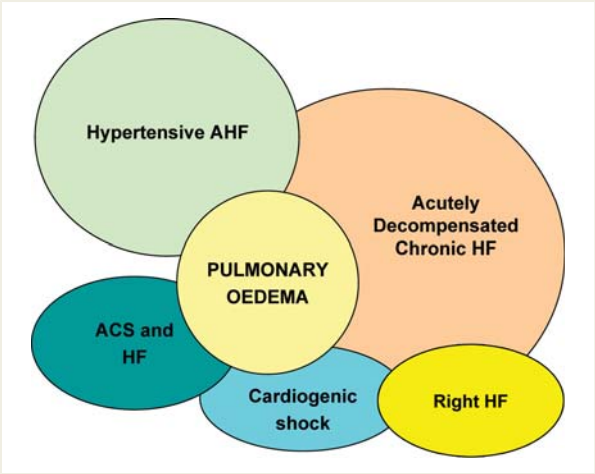

Figure 3 Clinical classification of acute heart failure. Modified from reference 205.

The response to appropriate therapy is rapid, and hospital mortality is low.

- **Cardiogenic shock**: is defined as evidence of tissue hypoperfusion induced by HF after adequate correction of preload and major arrhythmia. There are no diagnostic haemodynamic parameters. However, typically, cardiogenic shock is characterized by reduced systolic blood pressure (SBP; <90 mmHg or a drop of mean arterial pressure >30 mmHg) and absent or low urine output (<0.5 mL/kg/h). Rhythm disturbance are common. Evidence of organ hypoperfusion and pulmonary congestion develop rapidly.
- **Isolated right HF**: is characterized by a low output syndrome in the absence of pulmonary congestion with increased jugular venous pressure, with or without hepatomegaly, and low LV filling pressures.
- **ACS and HF**: many patients with AHF present with a clinical picture and laboratory evidence of an ACS.[206] Approximately 15% of patients with an ACS have signs and symptoms of HF. Episodes of acute HF are frequently associated with or precipitated by an arrhythmia (bradycardia, AF, VT).

Various classifications of acute HF are utilized in intensive cardiac care units. The Killip classification[57] is based on clinical signs following acute MI (see section Preamble and introduction). The Forrester classification[58] is also based on clinical signs and haemodynamic characteristics after acute MI. *Figure 4* presents a clinical classification modified from the Forrester classification.

Prognosis

The data from several recent AHF registries and surveys such as the EuroHeart Failure Survey II,[206] the ADHERE registry in the USA,[207,208] and the national surveys from Italy,[209] France,[210] and Finland[211] have been published. Many of the patients included in these registries were elderly with considerable cardiovascular and non-cardiovascular co-morbidity and a poor short- and long-term prognosis. ACS is the most frequent cause of acute new-onset HF. In-hospital mortality is especially high in patients with

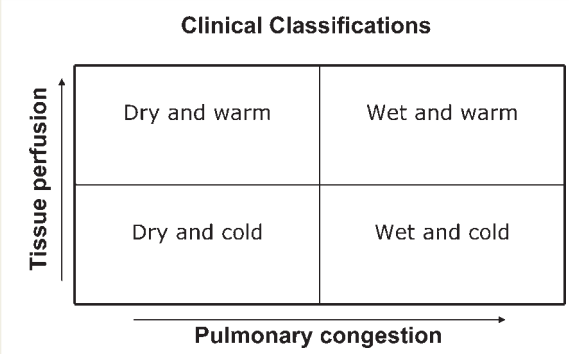

Figure 4 Evaluation of acutely decompensated chronic HF.

evidence of cardiogenic shock (from 40 to 60%). In contrast, patients with acute hypertensive HF have low in-hospital mortality, with patients usually discharged alive and frequently asymptomatic.

Median length of stay in hospital following admission due to AHF in the EuroHeart Survey II was 9 days. Registries indicate that almost half of the patients hospitalized with AHF are rehospitalized at least once within 12 months. Estimates of the combined outcome of death or rehospitalizations within 60 days of admission vary from 30 to 50%. Adverse prognostic indicators are similar to those in chronic HF (*Table 17*).[212]

Diagnosis of acute heart failure

The diagnosis of AHF is based on the presenting symptoms and clinical findings (see section Definition and diagnosis). Confirmation and refinement of the diagnosis is provided by appropriate investigations such as the history, physical examination, ECG, chest X-ray, echocardiography, and laboratory investigation, with blood gases and specific biomarkers. The diagnostic algorithm is similar for AHF developing *de novo* or as an episode of decompensation in chronic HF (see section Diagnostic techniques and *Figure 5*).

Initial evaluation

Systematic assessment of the clinical presentation is essential, with a focused history and appropriate physical examination. Assessment of peripheral perfusion, skin temperature, and venous filling pressures are important. Cardiac auscultation for systolic and diastolic murmurs as well as a third and fourth heart sounds (S3, S4) should be performed. Mitral insufficiency is extremely common in the acute phase. Significant aortic stenosis or insufficiency should be detected. Pulmonary congestion is detected by chest auscultation, with the presence of bibasal rales often with bronchial constriction over the lung fields usually indicating raised left heart filling pressure. Right heart filling pressures are assessed by evaluating jugular venous filling. Pleural effusions are common in acutely decompensated chronic HF.

The following investigations are considered appropriate in patients with AHF. However, the recommendations largely represent expert consensus opinion without adequate documented evidence. Class of recommendation I, level of evidence C applies unless otherwise stated.

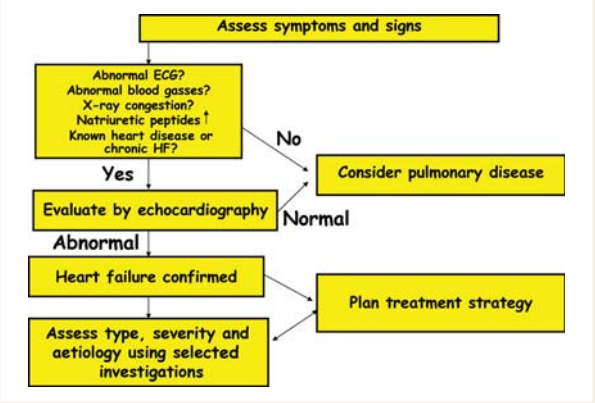

Figure 5 Evaluation of patients with suspected AHF.

Electrocardiogram (ECG)

The ECG provides essential information regarding heart rate, rhythm, conduction, and frequently aetiology. The ECG may indicate ischaemic ST segment changes suggestive of ST-segement elevation myocardial infarction (STEMI) or non-STEMI. Q waves indicate previous transmural infarction. Evidence of hypertrophy, bundle branch block, electrical dyssynchrony, prolonged QT interval, dysrhythmia, or perimyocarditis should be sought.

Chest X-ray

Chest X-ray should be performed as soon as possible at admission for all patients with AHF to assess the degree of pulmonary congestion and to evaluate other pulmonary or cardiac conditions (cardiomegaly, effusion, or infiltrates). The limitations of a supine film in an acutely ill patient should be noted.

Arterial blood gas analysis

Arterial blood gas analysis enables assessment of oxygenation (pO_2), respiratory function (pCO_2), and acid–base balance (pH), and should be assessed in all patients with severe respiratory distress. Acidosis due to poor tissue perfusion or CO_2 retention is associated with a poor prognosis. Non-invasive measurement with pulse oximetry can often replace arterial blood gas analysis but does not provide information on pCO_2 or acid–base status, and is unreliable in very low output syndromes or vasocontricted, shock states.

Laboratory tests

Initial diagnostic evaluation of patients with AHF includes full blood count, sodium, potassium, urea, creatinine, glucose, albumin, hepatic enzymes, and INR. Low sodium and high urea and creatinine serum levels are adverse prognostic factors in AHF. A small elevation in cardiac troponin may be seen in patients with AHF without ACS. Elevated troponin compatible with ACS is associated with an adverse prognosis.[213]

Natriuretic peptides

B-type natriuretic peptides (BNP and NT-proBNP) taken in the acute phase have a reasonable negative predictive value for excluding HF, although the evidence for this practice is not as extensive as with chronic HF (see section Definition and diagnosis). There is no consensus regarding BNP or NT-proBNP reference values in AHF. During 'flash' pulmonary oedema or acute MR, natriuretic peptide levels may remain normal at the time of admission. Increased BNP and NT-pro BNP levels on admission and before discharge carry important prognostic information.[59,214]

Echocardiography

Echocardiography with Doppler is an essential tool for the evaluation of the functional and structural changes underlying or associated with AHF. All patients with AHF should be evaluated as soon as possible. The findings will frequently direct treatment strategy. Echo/Doppler imaging should be used to evaluate and monitor regional and global left and right ventricular systolic function, diastolic function, valvular structure and function, pericardial pathology, mechanical complications of acute MI, and evidence of dyssynchrony. Non-invasive, semi-quantitative assessment of right and left ventricular filling pressures, stroke volume, and pulmonary artery pressures may influence treatment strategy. An echo/Doppler study, repeated as required during the hospital stay, may often obviate the need for invasive evaluation/monitoring.

Instrumentation and monitoring of patients in acute heart failure

Monitoring of the patient with AHF should be started as soon as possible after the arrival at the emergency unit, concurrent with ongoing diagnostic measures focused on determining the primary aetiology as well as the response to the initial treatment strategy.

Non-invasive monitoring

In all critically ill patients, monitoring the routine basic observations of temperature, respiratory rate, heart rate, BP, oxygenation, urine output, and the electrocardiogram is mandatory. A pulse oximeter should be used continuously in any unstable patient who is being treated with a fraction of inspired oxygen (FiO_2) that is greater than air, and the values recorded at regular intervals in patients receiving oxygen therapy for AHF.

Invasive monitoring

Arterial line

The indications for the insertion of an arterial catheter are the need for either continuous analysis of arterial BP due to haemodynamic instability, or the requirement for frequent arterial blood samples.

Class of recommendation IIa, level of evidence C

Central venous lines

Central venous lines provide access to the central circulation and are therefore useful for the delivery of fluids and drugs, and monitoring of the central venous pressure (CVP) and venous oxygen saturation (SVO_2), which provides an estimate of the body oxygen consumption/delivery ratio.

Class of recommendation IIa, level of evidence C

Pulmonary artery catheter

The insertion of a pulmonary artery catheter (PAC) for the diagnosis of AHF is usually unnecessary. A PAC can be useful to distinguish between a cardiogenic and non-cardiogenic mechanism in complex patients with concurrent cardiac and pulmonary disease, especially when echo/Doppler measurements are difficult to obtain. A PAC may be useful in haemodynamically unstable patients who are not responding as expected to traditional treatments.

The complication rate following insertion of a PAC increases with the duration of its utilization. It is critical to have clear objectives prior to insertion of the catheter. Pulmonary capillary wedge pressure is not an accurate reflection of LV end-diastolic pressure in patients with mitral stenosis, aortic regurgitation, pulmonary venous occlusive disease, ventricular interdependence, high airway pressure, respirator treatment, or a poorly compliant LV. Severe tricuspid regurgitation, frequently found in patients with AHF, can make the estimate of cardiac output measured by thermodilution unreliable.

Class of recommendation IIb, level of evidence B

Coronary angiography

In cases of AHF and evidence of ischaemia such as unstable angina or ACS, coronary angiography is indicated in patients without strong contraindications. Revascularization options (PCI/CABG) should be considered if technically possible in appropriate patients with an acceptable risk profile. Successful reperfusion treatment has been shown to improve prognosis.[215]

Class of recommendation I, level of evidence B

Since the majority of patients presenting with AHF have CAD, diagnosing CAD is important for decisions concerning medical therapy such as IIb/IIIa glycoprotein antagonists, oral antiplatelet agents, statins, and potential revascularization.

Organization of acute heart failure treatment

The immediate goals are to improve symptoms and to stabilize the haemodynamic condition (see *Table 27* and *Figure 6*). Treatment of hospitalized patients with AHF requires a well-developed treatment strategy with realistic objectives and a plan for follow-up that should be initiated prior to discharge. Many patients will require long-term treatment if the acute episode leads to chronic HF. The treatment of AHF should be followed-up by a HF management programme when available, as recommended in these guidelines.

Class of recommendation I, level of evidence B

Management

Multiple agents are used to manage AHF, but there is a paucity of clinical trials data and their use is largely empiric. Adequate long-term outcome data are not available. In the published AHF trials, most agents improve haemodynamics but no agent has been shown to reduce mortality. Potential limitations in these trials include the heterogeneous populations studied and the delay between hospital presentation and therapeutic intervention.

The following management options are considered appropriate in patients with AHF. However, the recommendations largely represent expert consensus opinion without adequate documentation from randomized clinical trials. Therefore, level of evidence C applies unless otherwise stated.

Table 27 Goals of treatment in acute heart failure

- **Immediate (ED/ICU/CCU)**
  - Improve symptoms
  - Restore oxygenation
  - Improve organ perfusion and haemodynamics
  - Limit cardiac/renal damage
  - Minimize ICU length of stay
- **Intermediate (in hospital)**
  - Stabilize patient and optimize treatment strategy
  - Initiate appropriate (life-saving) pharmacological therapy
  - Consider device therapy in appropriate patients
  - Minimize hospital length of stay
- **Long-term and pre-discharge management**
  - Plan follow-up strategy
  - Educate and initiate appropriate lifestyle adjustments
  - Provide adequate secondary prophylaxis
  - Prevent early readmission
  - Improve quality of life and survival

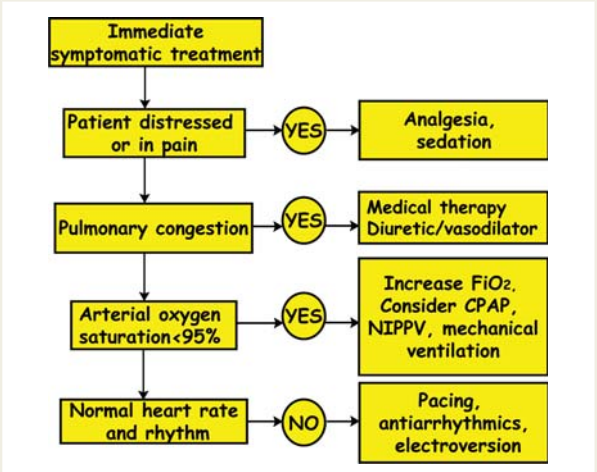

Figure 6 Initial treatment algorithm in AHF.

Oxygen

It is recommended to administer oxygen as early as possible in hypoxaemic patients to achieve an arterial oxygen saturation ≥95% (>90% in COPD patients). Care should be taken in patients with serious obstructive airways disease to avoid hypercapnia.

Class of recommendation I, level of evidence C

Non-invasive ventilation

Indications

Non-invasive ventilation (NIV) refers to all modalities that assist ventilation without the use of an endotracheal tube but rather with a sealed face-mask. NIV with positive end-expiratory pressure (PEEP) should be considered as early as possible in every patient with acute cardiogenic pulmonary oedema and hypertensive AHF as it improves clinical parameters including respiratory distress. NIV with PEEP improves LV function by reducing LV afterload. NIV should be used with caution in cardiogenic shock and right ventricular failure.

Class of recommendation IIa, level of evidence B

Key points

- Three recent meta-analyses reported that early application of NIV in patients with acute cardiogenic pulmonary oedema reduces both the need for intubation and short-term mortality. However, in 3CPO, a large RCT, NIV improved clinical parameters but not mortality.[216–219]
- Intubation and mechanical ventilation should be restricted to patients in whom oxygen delivery is not adequate by oxygen mask or NIV, and in patients with increasing respiratory failure or exhaustion as assessed by hypercapnia.

Contraindications

- Patients who cannot cooperate (unconscious patients, severe cognitive impairment, or anxiety)
- Immediate need of endotracheal intubation due to progressive life-threatening hypoxia
- Caution in patients with severe obstructive airways disease

How to use non-invasive ventilation

Initiation

- A PEEP of 5–7.5 cmH_2O should be applied first and titrated to clinical response up to 10 cmH_2O; FiO_2 delivery should be $\geq$0.40.

Duration

- Usually 30 min/h until patient's dyspnoea and oxygen saturation remain improved without continuous positive airway pressure (CPAP)

Potential adverse effects

- Worsening of severe right ventricular failure
- Drying of the mucous membranes with prolonged, continuous use
- Hypercapnia
- Anxiety or claustrophobia
- Pneumothorax
- Aspiration

Morphine and its analogues in acute heart failure

Morphine should be considered in the early stage of the treatment of patients admitted with severe AHF especially if they present with restlessness, dyspnoea, anxiety, or chest pain.[220–222] Morphine relieves dyspnoea and other symptoms in patients with AHF and may improve cooperation for the application of NIV. The evidence in favour of morphine use for AHF is limited.

- Intavenous boluses of morphine 2.5–5 mg may be administered as soon as the i.v. line is inserted in AHF patients. This dosing can be repeated as required.
- Respiration should be monitored.
- Nausea is common, and antiemetic therapy may be required.
- Caution in patients with hypotension, bradycardia, advanced AV block, or CO_2 retention.

Loop diuretics

Indications

- Administration of i.v. diuretics is recommended in AHF patients in the presence of symptoms secondary to congestion and volume overload (see *Table 28*).

Class of recommendation I, level of evidence B

Key points

- The symptomatic benefits and universal clinical acceptance of acute diuretic treatment has precluded formal evaluation in large-scale randomized clinical trials.[223–226]
- Patients with hypotension (SBP $<$90 mmHg), severe hyponatraemia, or acidosis are unlikely to respond to diuretic treatment.
- High doses of diuretics may lead to hypovolaemia and hyponatraemia, and increase the likelihood of hypotension on initiation of ACEIs or ARBs.
- Alternative treatment options such as IV vasodilators may reduce the need for high-dose diuretic therapy.

How to use a loop diuretic in acute heart failure

- The recommended initial dose is a bolus of furosemide 20–40 mg i.v. (0.5–1 mg of bumetanide; 10–20 mg of torasemide) at admission. Patients should be assessed frequently in the initial phase to follow urine output. The placement of a bladder catheter is usually desirable in order to monitor urinary output and rapidly assess treatment response.
- In patients with evidence of volume overload, the dose of i.v. furosemide may be increased according to renal function and a history of chronic oral diuretic use. In such patients, continuous infusion may also be considered after the initial starting dose. The total furosemide dose should remain $<$100 mg in the first 6 h and 240 mg during the first 24 h.

Combination with other diuretics

Thiazides in combination with loop diuretics may be useful in cases of diuretic resistance. In case of volume-overloaded AHF, thiazides (hydrochlorothiazide 25 mg p.o.) and aldosterone antagonists (spironolactone, eplerenone 25–50 mg p.o.) can be used in association with loop diuretics. Combinations in low doses are often more effective with fewer side-effects than with the use of higher doses of a single drug.

Table 28 Indications and dosing of diuretics in acute heart failure

Fluid retention	Diuretic	Daily dose (mg)	Comments
Moderate	Furosemide or	20–40	Oral or i.v. according to clinical symptoms
	bumetanide or	0.5–1	Titrate dose according to clinical response
	torasemide	10–20	Monitor K, Na, creatinine, blood pressure
Severe	Furosemide	40–100	i.v. Increase dose
	Furosemide infusion	(5–40 mg/h)	Better than very high bolus doses
	Bumetanide	1–4	Oral or i.v.
	Torasemide	20–100	Oral
Refractory to loop diuretic	Add hydrochlorothiazide	50–100	Combination better than very high dose of loop diuretics
	or metolazone	2.5–10	More potent if creatinine clr < 30 ml/min
	or spironolactone	25–50	Spironolactone best choice if no renal failure and normal or low K
With alkalosis	Acetazolamide	500	i.v.
Refractory to loop diuretics and thiazides	Add dopamine (renal vasodilation) or dobutamine		Consider ultrafiltration or haemodialysis if co-existing renal failure Hyponatraemia

Table 29 Indications and dosing of i.v.vasodilators in acute heart failure

Vasodilator	Indication	Dosing	Main side-effects	Other
Nitroglycerine	Pulmonary congestion/oedema BP >90 mmHg	Start 10–20 μg/min, increase up to 200 μg/min	Hypotension, headache	Tolerance on continuous use
Isosorbide dinitrate	Pulmonary congestion/oedema BP >90 mmHg	Start with 1 mg/h, increase up to 10 mg/h	Hypotension, headache	Tolerance on continuous use
Nitroprusside	Hypertensive HF congestion/ oedema BP >90 mmHg	Start with 0.3 μg/kg/min and increase up to 5 μg/kg/min	Hypotension, isocyanate toxicity	Light sensitive
Nesiritide*	Pulmonary congestion/oedema BP >90 mmHg	Bolus 2 μg/kg + infusion 0.015–0.03 μg/kg/min	Hypotension	

*Not available in many ESC countries.

Potential adverse effects of loop diuretics

- Hypokalaemia, hyponatraemia, hyperuricaemia
- Hypovolaemia and dehydration; urine output should be assessed frequently
- Neurohormonal activation
- May increase hypotension following initiation of ACEI/ARB therapy

Vasopressin antagonists

Several types of vasopressin receptors have been identified: V1a receptors mediate vasoconstriction, whereas stimulation of V2 receptors located in the kidneys promotes water re-absorption. The two most extensively investigated vasopressin antagonists are conivaptan (a dual V1a/V2 receptor antagonist) in hyponatraemia, and tolvaptan (an oral, selective antagonist of the V2 receptor) in AHF. In EVEREST, tolvaptan relieved symptoms associated with AHF and promoted weight loss in the acute phase, but did not reduce mortality or morbidity at 1 year.[227]

Vasodilators

Vasodilators are recommended at an early stage for AHF patients without symptomatic hypotension, SBP <90 mmHg or serious obstructive valvular disease. The recommended dosage of vasodilators is presented in *Table 29*.

Class of recommendation I, level of evidence B

Indications

Intravenous nitrates and sodium nitroprusside are recommended in AHF patients with SBP >110 mmHg and may be used with caution in patients with SBP between 90 and 110 mmHg. These agents decrease SBP, decrease left and right heart filling pressures and systemic vascular resistance, and improve dyspnoea. Coronary blood flow is usually maintained unless diastolic pressure is compromised.[228,229]

Key points

- Vasodilators relieve pulmonary congestion usually without compromising stroke volume or increasing myocardial oxygen demand in acute HF, particularly in patients with ACS.
- Calcium antagonists are not recommended in the management of AHF.
- Any vasodilator should be avoided in AHF patient with SBP <90 mmHg as it may reduce central organ perfusion.
- Hypotension should be avoided, especially in patients with renal dysfunction.
- Patients with aortic stenosis may demonstrate marked hypotension following the initiation of i.v. vasodilator treatment.

How to use vasodilators in AHF

Nitrates (nitroglycerine isosorbide mononitrate, and isosorbide dinitrate), sodium nitroprusside, and nesiritide are used as continuous infusion. Intravenous nitroglycerine is the agent most widely used in AHF, with a predominantly venodilator effect. Intavenous nitroprusside is a potent balanced vasodilator with combined preload and afterload reduction. Intavenous nesiritide, a recombinant form of human B-type natriuretic peptide, is a venous and arterial vasodilator with a combined modest diuretic and natriuretic effect.

- It is recommended to administer nitroglycerine in the early phase of AHF frequently followed by a continuous infusion of nitroglycerine, nitroglycerine spray of 400 μg (2 puffs) every 5–10 min, buccal nitrate (isosorbide dinitrate 1 or 3 mg), or 0.25–0.5 mg sublingual nitroglycerine.
- The initial recommended dose of i.v. nitroglycerin is 10–20 μg/min, increased in increments of 5–10 μg/min every 3–5 min as needed.
- Slow titration of i.v. nitrates and frequent BP measurement is recommended to avoid large drops in SBP. An arterial line is not routinely required but will facilitate titration in patients with borderline pressures.
- Intravenous nitroprusside should be administered with caution. The initial infusion rate should be 0.3 μg/kg/min with titration up to 5 μg/kg/min. An arterial line is recommended.
- Intravenous nesiritide may be initiated with or without a bolus infusion with infusion rates from 0.015 to 0.03 μg/kg/min. Non-invasive BP measurements are usually adequate. Combination with other i.v. vasodilators is not recommended. Nesiritide is not available in most European countries.

Potential adverse effects

Headache is frequently reported with nitrates. Tachyphylaxis is common after 24–48 h, necessitating incremental dosing with nitrates. Intravenous nitroprusside should be used cautiously in patients with ACS, as abrupt hypotension is not infrequent. Hypotension may also occur with i.v. nitroglycerine or nesiritide infusion.

Inotropic agents (*Table 30*)

Inotropic agents should be considered in patients with low output states, in the presence of signs of hypoperfusion or congestion despite the use of vasodilators and/or diuretics to improve symptoms. *Figure 7* describes a treatment algorithm based on the level of SBP, and *Figure 8* describes the treatment algorithm based on a clinical assessment of patients filling pressures and perfusion.

Class of recommendation IIa, level of evidence B

Indications for inotropic therapy

Inotropic agents should only be administered in patients with low SBP or a low measured cardiac index in the presence of signs of hypoperfusion or congestion.[230–237] Signs of hypoperfusion include cold, clammy skin, in patients who are vasoconstricted with acidosis, renal impairment, liver dysfunction, or impaired mentation. Therapy should be reserved for patients with dilated, hypokinetic ventricles.

When needed, inotropic agents should be administered as early as possible and withdrawn as soon as adequate organ perfusion is restored and/or congestion reduced. Although inotropes may acutely improve the haemodynamic and clinical status of patients with AHF, they may promote and accelerate some pathophysiological mechanisms, causing further myocardial injury and leading to increased short- and long-term mortality.

In some cases of cardiogenic shock, inotropic agents may stabilize patients at risk of progressive haemodynamic collapse or serve as a life-sustaining bridge to more definitive therapy such as mechanical circulatory support, ventricular assist devices, or cardiac transplantation. Infusion of most inotropes is accompanied by an increased incidence of both atrial and ventricular arrhythmias. In patients with AF, dobutamine/dopamine may facilitate conduction through the AV node and lead to tachycardia. Continuous clinical monitoring and ECG telemetry is required.

Dobutamine

Dobutamine, a positive inotropic agent acting through stimulation of β_1-receptors to produce dose-dependent positive inotropic and chronotropic effects, is usually initiated with a 2–3 μg/kg/min infusion rate without a loading dose. The infusion rate may then be progressively modified according to symptoms, diuretic response, or clinical status. Its haemodynamic actions are dose-related, which can be increased to 15 μg/kg/min. BP should be monitored, invasively or non-invasively. In patients receiving β-blocker therapy, dobutamine doses may have to be increased to as high as 20 μg/kg/min to restore its inotropic effect.[234] The elimination of the drug is rapid after cessation of infusion. Care should be exercised in weaning patients from dobutamine infusion. Gradual tapering (i.e. decrease in dosage by steps of 2 μg/kg/min) and simultaneous optimization of oral therapy are essential.

Class of recommendation IIa, level of evidence B

Dopamine

Dopamine, which also stimulates β-adrenergic receptors both directly and indirectly with a consequent increase in myocardial contractility and cardiac output, is an additional inotropic agent. Infusion of low doses of dopamine (≤2–3 mg/kg/min) stimulates dopaminergic receptors but has been shown to have limited effects on diuresis. Higher doses of dopamine may be used to

Table 30 Dosing of positive inotropic agents in acute heart failure

	Bolus	Infusion rate
Dobutamine	No	2–20 μg/kg/min (β+)
Dopamine	No	<3 μg/kg/min: renal effect (δ+) 3–5 μg/kg/min: inotropic (β+) >5 μg/kg/min: (β+), vasopressor (α+)
Milrinone	25–75 μg/kg over 10-20 min	0.375–0.75 μg/kg/min
Enoximone	0.25–0.75 mg/kg	1.25–7.5 μg/kg/min
Levosimendan*	12 μg/kg over 10 min (optional)**	0.1 μg/kg/min which can be decreased to 0.05 or increased to 0.2 μg/kg/min
Norepinephrine	No	0.2–1.0 μg/kg/min
Epinephrine	Bolus: 1 mg can be given i.v. during resuscitation, repeated every 3–5 min	0.05–0.5 μg/kg/min

*This agent also has vasodilator properties.
**In hypotensive patients (SBP <100 mmHg) initiation of therapy without a bolus is recommended.

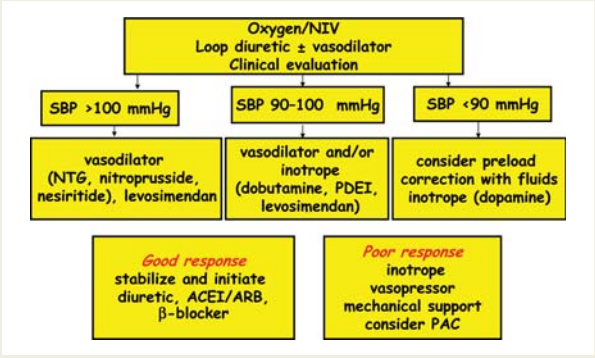

Figure 7 AHF treatment strategy according to systolic blood pressure.

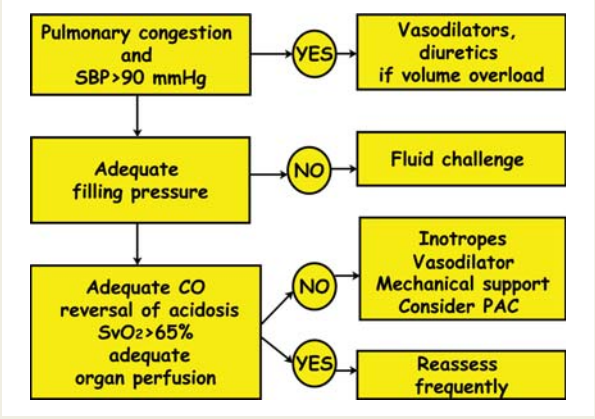

Figure 8 AHF treatment strategy according to LV filling pressure.

maintain SBP, but with an increasing risk of tachycardia, arrhythmia, and α-adrenergic stimulation with vasoconstriction. Dopamine and dobutamine should be used with caution in patients with a heart rate >100 b.p.m.[232] The alpha stimulation at higher doses may lead to vasoconstriction and elevated systemic vascular resistance. Low-dose dopamine is frequently combined with higher doses of dobutamine.

Class of recommendation IIb, level of evidence C

Milrinone and enoximone

Milrinone and enoximone are the two type III phosphodiesterase inhibitors (PDEIs) used in clinical practice. The agents inhibit the breakdown of cyclic AMP and have inotropic and peripheral vasodilating effects, with an increase in cardiac output and stroke volume, and a concomitant decline in pulmonary artery pressure, pulmonary wedge pressure, and systemic and pulmonary vascular resistance. As their cellular site of action is distal to the β-adrenergic receptors, the effects of PDEIs are maintained during concomitant β-blocker therapy.[236] Milrinone and enoximone are administered by a continuous infusion possibly preceded by a bolus dose in patients with well-preserved BP. Caution should be used with the administration of PDEIs in patients with CAD, as it may increase medium-term mortality.[231]

Class of recommendation IIb, level of evidence B

Levosimendan

Levosimendan is a calcium sensitizer that improves cardiac contractility by binding to troponin-C in cardiomyocytes. It exerts significant vasodilatation mediated through ATP-sensitive potassium channels and has mild PDE inhibitory action. Levosimendan infusion in patients with acutely decompensated HF increases cardiac output and stroke volume and reduces pulmonary wedge pressure, systemic vascular resistance, and pulmonary vascular resistance. The haemodynamic response to levosimendan is

maintained over several days. Levosimendan may be effective in patients with decompensated chronic HF. In that the inotropic effect is independent of β-adrenergic stimulation, it represents an alternative for patients on β-blocker therapy. Levosimendan treatment is associated with a slight increase in heart rate and a decrease in the BP, especially if a loading dose is administered.[235,237]

Levosimendan may be administered as a bolus dose (3–12 μg/kg) during 10 min followed by a continuous infusion (0.05–0.2 μg/kg/min for 24 h). The infusion rate may be increased once stability is confirmed. In patients with SBP <100 mmHg, the infusion should be started without a bolus dose to avoid hypotension.

Class of recommendation IIa, level of evidence B

Vasopressors

Vasopressors (norepinephrine) are not recommended as first-line agents and are only indicated in cardiogenic shock when the combination of an inotropic agent and fluid challenge fails to restore SBP >90 mmHg, with inadequate organ perfusion, despite an improvement in cardiac output. Patients with sepsis complicating AHF may require a vasopressor. Since cardiogenic shock is usually associated with a high systemic vascular resistance, all vasopressors should be used with caution and discontinued as soon as possible. Noradrenaline might be used with any of above-mentioned inotropic agents in cardiogenic shock, ideally perfused through a central line. Caution is advised with dopamine that already exerts a vasopressor effect. Epinephrine is not recommended as an inotrope or vasopressor in cardiogenic shock and should be restricted to use as rescue therapy in cardiac arrest.

Class of recommendation IIb, level of evidence C

Cardiac glycosides

In AHF, cardiac glycosides produce a small increase in cardiac output and a reduction of filling pressures. It may be useful to slow ventricular rate in rapid AF.

Class of recommendation IIb, level of evidence C

Algorithm for acute heart failure management

After the initial assessment, all patients should be considered for oxygen therapy and NIV. The goal of treatment in the pre-hospital setting or at the emergency room is to improve tissue oxygenation and optimize haemodynamics in order to improve symptoms and permit interventions (see *Figure 6*). A specific treatment strategy should be based on distinguishing the clinical conditions as described below:

- **Decompensated chronic HF**: vasodilators along with loop diuretics are recommended. Consider higher dose of diuretics in renal dysfunction or with chronic diuretic use. Inotropic agents are required with hypotension and signs of organ hypoperfusion.
- **Pulmonary oedema**: morphine is usually indicated, especially when dyspnoea is accompanied by pain and anxiety. Vasodilators are recommended when BP is normal or high, and diuretics in patients with volume overload or fluid retention. Inotropic agents are required with hypotension and signs of organ hypoperfusion. Intubation and mechanical ventilation may be required to achieve adequate oxygenation.
- **Hypertensive HF**: vasodilators are recommended with close monitoring and low-dose diuretic treatment in patients with volume overload or pulmonary oedema.
- **Cardiogenic shock**: a fluid challenge if clinically indicated (250 mL/10 min) followed by an inotrope if SBP remains <90 mmHg is recommended. If the inotropic agent fails to restore SBP and signs of organ hypoperfusion persist, norepinephrine may be added with extreme caution. An intra-aortic balloon pump (IABP) and intubation should be considered. LVADs may be considered for potentially reversible causes of acute HF as a bridge to treatment response (i.e. surgery or recovery).
- **Right HF**: a fluid challenge is usually ineffective. Mechanical ventilation should be avoided. Inotropic agents are required when there are signs of organ hypoperfusion. Pulmonary embolism and right ventricular MI should be suspected.
- **AHF and ACS**: all patients with ACS and signs and symptoms of HF should undergo an echocardiographic study to assess systolic and diastolic ventricular function, valvular function, and rule out other cardiac abnormalities or mechanical complications of MI.

Class of recommendation I, level of evidence C

In ACS complicated by AHF, early reperfusion may improve prognosis (Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation. *Eur Heart J* 2008, doi:10.1093/eurheartj/ehn416, in press). If neither PCI nor surgery is readily available or can only be provided after a delay, early fibrinolytic therapy is recommended in patients with STEMI. Urgent surgery is indicated in patients with mechanical complications after AMI. In cardiogenic shock caused by ACS, insertion of an IABP, coronary angiography, and revascularization (primary PCI) should be considered as soon as possible.

Class of recommendation I, level of evidence C

Management of patients with acutely decompensated chronic heart failure treated with β-blockers and ACEIs/ARBs

ACEIs are not indicated in the early stabilization of patients with AHF. However, as these patients are at high risk for development of chronic HF, ACEIs/ARBs have an important role in early management of AHF patients and acute MI, particularly in the presence of HF and/or evidence of LV systolic dysfunction. These agents attenuate remodelling, and reduce morbidity and mortality. There is no consensus on the ideal timing for initiation of ACEI/ARB therapy in AHF. In general, it is recommended that treatment with these agents should be initiated before discharge from hospital. Patients on ACEIs/ARBs admitted with worsening HF should be continued on this treatment whenever possible.

Class of recommendation I, level of evidence A

In patients with acutely decompensated HF, the dose of β-blocker may need to be reduced temporarily or omitted, although generally treatment should not be stopped, unless the patient is clinically

unstable with signs of low output. Treatment may be interrupted or reduced in the presence of complications (bradycardia, advanced AV block, bronchospasm, or cardiogenic shock) or in cases of severe AHF and an inadequate response to initial therapy. In patients following an AMI, with symptoms of HF or evidence of LV dysfunction, β-blockers should also be initiated early and preferably prior to discharge. In patients admitted with AHF, β-blockers should be considered when the patient has been stabilized on an ACEI or ARB and preferably initiated before hospital discharge.

Class of recommendation IIa, level of evidence B

Implementation and delivery of care

In many European countries, >2% of the total healthcare budget is related to HF management, and up to 70% of this cost is related to hospitalizations.[238] Optimization of therapy is often not achieved either in primary or in secondary care, even during hospitalization. In addition, discharge planning and follow-up after hospitalization are frequently insufficient, leading to poor self-care behaviour, inadequate support for the patients, and suboptimal treatment. Poor or non-adherence to medication, diet, or symptom recognition is common[70,71] and may be responsible for over one-third of the hospital readmissions. Management programmes are designed to improve outcomes through structured follow-up with patient education, optimization of medical treatment, psychosocial support, and access to care.

Management of patients with HF exemplifies the relevance of a shift of the emphasis of management away from acute and subacute episodes of illness toward chronic conditions where the nature of professional and patient transactions is distinctly different. *Table 31* summarises the goals and measures involved during potential phases of this transition.

Heart failure management programmes

- Heart failure management programmes are recommended for patients with HF recently hospitalized and for other high-risk patients.

Class of recommendation I, level of evidence A

HF management programmes are structured as a multidisciplinary care approach that coordinate care along the continuum of HF and throughout the chain of care delivered by various services within the healthcare systems. Multidisciplinary teams in HF may include nurses, cardiologists, primary care physicians, physical therapists, dieticians, social workers, psychologists, pharmacists, geriatricians, and other healthcare professionals and services. The content and structure of HF management programmes vary widely in different countries and healthcare settings, and are tailored to meet local needs.[239]

Many programmes focus on symptomatic, hospitalized patients with HF since they have a poorer prognosis and are at a higher risk for readmissions. An outpatient visit, early after discharge, is recommended to assess clinical status, identify objectives, and design an effective treatment strategy. Although it seems reasonable to assume that more intensive programmes should be more effective than less intensive programmes, the available studies do not unequivocally show a reduction in admission rates with more intensified interventions,[240,241] and low intensity interventions compared with no structured follow-up has been shown to improve event-free survival.[242,243].

If possible, patients should learn to recognize symptoms and practise self-care measures (see section Non-pharmacological management). Nurses are often involved in drug titration, and titration protocols and treatment algorithms should be employed.[244] Programmes may also be involved in the management of patients with an implanted device (CRT/ICD). Increased access to care through

Table 31 Treatment goals and strategies during the course of the patient's journey

Phase	Diagnostic strategy	Action	Goals	Players
Acute	Assess clinical status Identify cause of symptoms	Treat and stabilize Initiate monitoring Plan required interventions	Stabilize, admit, and triage to appropriate department	Paramedics Primary care/ER physicians Intensivists Nurses Cardiologists
Subacute	Assess cardiac function Identify aetiology and co-morbidities	Initiate chronic medical treatment Perform additional diagnostics Perform indicated procedures	Shorten hospitalization Plan post-discharge follow-up	Hospital physicians Cardiologists CV nurses HF Management team
Chronic	Target symptoms, adherence, and prognosis Identify decompensation early	Optimize pharmacological and device treatment Support self-care behaviour Remote monitoring	Reduce morbidity and mortality	Primary care physicians HF Management team Cardiologists
End of life	Identify patient concerns and symptoms	Symptomatic treatment Plan for long-term care	Palliation Provide support for patients and family	Palliative care team

daily telephone calls to a HF nurse provides reassurance and allows patients the opportunity to discuss symptoms, treatment, side-effects, and self-care behaviour. Contact with the programme can be initiated during hospitalization, at discharge, during the first weeks after discharge, or as a request for consultation from primary care.

It is recommended that HF management programmes include the components shown in *Table 32*. Adequate education is essential.[245,246] Remote management is an emerging field within the broader context of HF management programmes, and extends the reach of individualized care to the large group of individuals unable to access traditional programmes of care.

Telephone support is a form of remote management that can be provided through scheduled calls from a HF nurse or physician, or through a telephone service, which the patients can contact if questions arise or symptoms of deterioration occur. Telemonitoring is another form of management that allows daily monitoring of symptoms and signs measured by patients, family, or caregivers at home while allowing patients to remain under close supervision.[247] Telemonitoring equipment may include recording BP, heart rate, ECG, oxygen saturation, weight, symptom response systems, medication adherence, device control and video consultation equipment—all of which can be installed in the patient's home. There is no consensus regarding which variables are most helpful to monitor, and new equipment with additional monitoring parameters and more sophisticated technology is under development.[247] There are also internal monitoring devices capable of delivering remote physiological monitoring (see section Devices and surgery).

Cardiac rehabilitation, as multifaceted and multidisciplinary interventions, has been proven to improve functional capacity, recovery, and emotional well-being, and to reduce hospital readmissions.[248]

Key evidence

- Several meta-analyses based on >8000 patients have evaluated the effect of multidisciplinary, often nurse-led, interventions with follow-up and patient education combined with optimization of medical treatment. The meta-analyses demonstrate that home-based follow-up or follow-up in a clinic setting significantly reduced hospitalization. The risk reduction ranged between 16 and 21%. Mortality was also significantly reduced.
- A large multicentre study evaluating the effect of education and an intense support programme by HF nurses on top of frequent visits with cardiologist did not show a reduction in the combined primary end-point of HF hospitalizations and mortality.[241]
- HF management programmes are likely to be cost-effective in that they reduce hospital readmissions and can be established on a relatively modest budget.[97]
- It has not been established which of the various models of care is optimal. Both clinic- and home-based models seem to be equally effective.[249] Face-to-face visits with a HF nurse have been shown to have large effects on outcomes.[250] Accurate assessment of local conditions and needs is essential. Advantages and disadvantages with each model are summarized in *Table 33*.
- A recent meta-analysis comparing predominantly telephone-based vs. face-to-face programmes of care suggested that the latter were more efficacious in reducing the risk of all-cause readmission and mortality.[97] The most contemporary meta-analysis of 14 randomized trials involving 4264 patients incorporating sophisticated models of remote HF management demonstrated 21 and 20% significant reductions in the risk of a HF-related admission and all-cause mortality, respectively.[247]
- The organization of a HF management programme should be based on patient needs, financial resources, available personnel, and administrative policies. As delivery of care varies in Europe, structured care needs to be adapted to local priorities and infrastructure.

Table 32 Recommended components of heart failure management programmes

- Multidisciplinary approach frequently led by HF nurses in collaboration with physicians and other related services
- First contact during hospitalization, early follow-up after discharge through clinic and home-based visits, telephone support, and remote monitoring
- Target high-risk, symptomatic patients
- Increased access to healthcare (telephone, remote monitoring, and follow-up)
- Facilitate access during episodes of decompensation
- Optimized medical management
- Access to advanced treatment options
- Adequate patient education with special emphasis on adherence and self-care management
- Patient involvement in symptom monitoring and flexible diuretic use
- Psychosocial support to patients and family and/or caregiver

Palliative care for patients with heart failure

- Patients with clinical features of advanced HF who continue to experience symptoms refractory to optimal evidence-based therapy have a poor short-term prognosis and should be considered appropriate for a structured palliative care approach. Psychological symptoms such as anxiety need to be addressed.

Class of recommendation I, level of evidence C

Features that should trigger such consideration and the proposed steps in the process of providing palliative care are presented in *Table 34*.

Advanced HF has a very poor 1-year survival rate, and the prognosis is worse than for most common forms of cancer.[34] However, in most European countries, patients with end-stage HF are infrequently referred to specialist palliative care. HF has an unpredictable disease trajectory and it is often difficult to identify a specific time point to introduce palliative care to HF management. Interventions should focus on improvement in quality of life, control of symptoms, early detection and treatment of episodes of deterioration, and on pursuing a holistic approach to patient

Table 33 Advantages and disadvantages of different models of heart failure programmes

	Advantages	Disadvantages
Clinic visits	• Convenient with medical expertise, facilities and equipment available. • Facilitates diagnostic investigation and adjustments of treatment strategy	• Frail, non-ambulatory patients not suitable for out-patient follow-up
Home care	• Access to immobile patients • More reliable assessment of the patient's needs, capabilities and adherence to treatment in their own home environment • Convenient for a follow-up visit shortly after hospitalization	• Time consuming travel for the HF team • Transportation and mobile equipment required • Nurses face medical responsibilities alone and may have difficulty contacting the responsible physician
Telephone support	• Low cost, time saving and convenient both for the team and the patient	• Difficult to assess symptoms and signs of heart failure and no tests can be performed • Difficult to provide psychosocial support, adjust treatment and educate patients
Remote monitoring	• Facilitates informed clinical decisions • Need is increasing as care shifts into patients' homes • New equipment and technology becoming rapidly available	• Requires education on the use of the equipment • Time-consuming for HF team • Difficult for patients with cognitive disability • Most helpful measurements not known

Table 34 Goals and steps in the process of providing palliative care in patients with heart failure

Patient features	>1 episode of decompensation/6 months despite optimal tolerated therapy Need for frequent or continual IV support Chronic poor quality of life with NYHA IV symptoms Signs of cardiac cachexia Clinically judged to be close to the end of life
Confirm diagnosis	Essential to ensure optimal treatment.
Patient education	Principles of self-care maintenance and management of HF
Establish an Advanced Care Plan	Designed with the patient and a family member. Reviewed regularly and includes the patients' preferences for future treatment options
Services should be organised	The patients' care within the multidisciplinary team, to ensure optimal pharmacological treatment, self-care management and to facilitate access to supportive services.
Symptom Management	Requires frequent assessment of patients' physical, psychological, social and spiritual needs. Patients frequently have multiple co-morbidities that need to be identified.
Identifying end-stage heart failure	Confirmation of end-stage HF is advisable to ensure that all appropriate treatment options have been explored a plan for the terminal stage of illness should be agreed upon.
Breaking bad news to the patient and family	Explaining disease progression and a change in treatment emphasis is a sensitive issue and must be approached with care.
Establishing new goals of care	End-of-life care should include avoidance of circumstances which may detract from a peaceful death. All current pharmacological treatment and device programmes should be considered. Resuscitation orders should be clear.

care encompassing physical, psychological, social, and spiritual well-being.

Liaison between specialist palliative care and the HF team, or the primary care physician in a shared care approach, is encouraged to address and coordinate patients' care needs optimally. Members of the team may include a patient care coordinator, general practitioner, cardiologist, HF nurse, palliative care physician, psychologist/psychotherapist, physiotherapist, dietician, and spiritual advisor. Although the prognosis and severity of patients' symptom may differ, the essential components of a successful palliative care programme are similar to those of HF management programmes.[251,252]

Gaps in evidence

Clinicians responsible for managing patients with HF must frequently make treatment decisions without adequate evidence or consensus expert opinion. The following is a shortlist of selected, common issues that deserve to be addressed in future clinical research.

- Females and the elderly have not been adequately represented in clinical trials and there is a need for further evaluation of treatments in these two populations.

Diagnosis and co-morbidity

- Is there a diagnostic role for natriuretic peptide assay in patients with HFPEF?
- Does any specific treatment of the following co-morbidities in patients with HF reduce morbidity and mortality?
  - renal dysfunction
  - anaemia
  - diabetes
  - depression
  - disordered breathing during sleep

Non-pharmacological, non-interventional therapy

- How can adherence in HF be improved?
- Is salt restriction beneficial in HF?
- Does exercise training improve survival in HF?
- Can cardiac cachexia be prevented or treated?

Pharmacological therapy

- Which pharmacological agents reduce morbidity and mortality in patients with an EF between 40 and 50% or HFPEF?
- Is aspirin use associated with a higher risk of HF hospitalization?

In patients with heart failure and systolic dysfunction

- Should ACEIs always be prescribed before β-blockers?
- Should an aldosterone antagonist or an ARB be added next in symptomatic patients on an ACEI and a β-blocker?
- Does tailoring HF therapy according to plasma natriuretic peptide concentrations reduce morbidity and mortality?
- Does an aldosterone antagonist reduce morbidity and mortality in patients with mild symptoms (NYHA class II)?
- Is quadruple therapy (ACEI, ARB, aldosterone antagonist, and β-blocker) better at reducing morbidity and mortality than use of three of these agents?

Intervention

- Does revascularization reduce morbidity and mortality in patients with HF, systolic dysfunction, and CAD?
- Does revascularization in patients with hibernating myocardium improve clinical outcomes?
- What criteria should be used in evaluating patients with HF and aortic stenosis/regurgitation or mitral regurgitation for valvular surgery?

Devices

- In patients with HF and a wide QRS complex, which patient characteristics should lead to a CRT-D being preferred over a CRT-P?
- Is there any role for echocardiographic assessment of dyssynchrony in the selection of patients for CRT?
- Does CRT improve clinical outcomes in patients with a low LVEF, a wide QRS, but mild symptoms (NYHA class II)?
- Does CRT improve clinical outcomes in patients with a low LVEF, severe symptoms (NYHA class III/IV), and a QRS width <120 ms?
- Does an ICD improve clinical outcomes in HF with an EF $>35\%$?
- How should patients be selected for bridge to recovery with an LVAD?
- Do LVADs provide an alternative treatment to transplantation in advanced heart failure?

Arrhythmias

- Does restoring sinus rhythm reduce morbidity and mortality in patients with HF, AF, and either systolic dysfunction or HFPEF?

Acute heart failure

- What is the role of NIV in AHF?
- Which is the most efficacious vasodilator in AHF in terms of reducing morbidity and mortality?
- Which is the most efficacious inotrope in AHF in terms of reducing morbidity and mortality?
- How should β-blocker treatment be managed in patients with acute decompensation?
- Does ultrafiltration expedite recovery and discharge in patients with AHF and volume overload?

Implementation

- Which components of HF management programmes are most important for reducing morbidity and mortality?
- Do HF management programmes reduce morbidity and mortality in patients with HFPEF?
- What aspects of remote monitoring might best detect early decompensation?

Detailed evidenced tables for treatment with ACEIs, ARBs, β-blockers, and devices are available on the Guidelines Section of the ESC website http://www.escardio.org/guidelines

The CME text 'ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008' is accredited by the European Board for Accreditation in Cardiology (EBAC) for '5' hours of External CME credits. Each participant should claim only those hours of credit that have actually been spent in the educational activity. EBAC works in cooperation with the European Accreditation Council for Continuing Medical Education (EACCME), which is an institution of the European Union of Medical Specialists (UEMS). In compliance with EBAC/EACCME guidelines, all authors participating in this programme have disclosed potential conflicts of interest that might cause a bias in the article. The Organizing Committee is responsible for ensuring that all potential conflicts of interest relevant to the programme are declared to the participants prior to the CME activities. CME questions for this article are available at: *European Heart Journal* http://cme.oxfordjournals.org/cgi/hierarchy/oupcme_node;ehj and *European Society of Cardiology* http://www.escardio.org/knowledge/guidelines.

Glossary

ACC	American College of Cardiology
ACE	angiotensin-converting enzyme
ACEI	angiotensin-converting enzyme inhibitor
ACS	acute coronary syndrome
AF	atrial fibrillation
AHA	American Heart Association
AHF	acute heart failure
ANA	antinuclear antibody
AR	aortic regurgitation
ARB	angiotensin receptor blocker
ARR	absolute risk reduction
AS	aortic stenosis
ATP	adenosine triphosphate
AV	atrioventricular
AVP	arginine vasopressin
b.i.d.	twice a day
BNP	B-type natriuretic peptide
BP	blood pressure
b.p.m.	beats per minute
BUN	blood urea nitrogen
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CCU	coronary care unit
CHF	chronic heart failure
Class 1c	Vaughan Williams antiarrhythmic classification
CMR	cardiac magnetic resonance
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
CR	sustained release
CRP	C-reactive protein
CRT	cardiac resynchronization therapy
CRT-D	cardiac resynchronization therapy - defibrillator
CRT-P	cardiac resynchronization therapy - pacemaker
CT	computer tomography
DDD	dual chamber pacing
DCM	dilated cardiomyopathy
dL	decilitre
DM	diabetes mellitus
EASD	European Association for the Study of Diabetes
ECG	electrocardiogram
ED	emergency department
EF	ejection fraction
EMB	endomyocardial biopsy
FiO_2	fraction of inspired oxygen
GFR	glomerular filtration rate
h	hour
HF	heart failure
HFPEF	heart failure with preserved ejection fraction
H-ISDN	hydralazine and isosorbide dinitrate
HIV	human immunodeficiency virus
IABP	intra-aortic balloon pump
ICD	implantable cardioverter defibrillator
ICU	intensive care unit
INR	international normalized ratio
ISDN	isosorbide dinitrate
i.v.	intravenous
JVP	jugular venous pressure
LBBB	left bundle branch block
LV	left ventricular
LVAD	left ventricular assist device
LVEF	left ventricular ejection fraction
MI	myocardial infarction
mg	milligrams
mmHg	millimetres of mercury
mmol	millimole
MR	mitral regurgitation
ms	millisecond
ng/mL	nanograms per millilitre
NIPPV	noninvasive positive pressure ventilation
NIV	non-invasive ventilation
NNT	number needed to treat
NSAID	non-steroidal anti-inflammatory drug
NTG	nitroglycerine
NT-proBNP	N-terminal pro B-type natriuretic peptide
NYHA	New York Heart Association
o.d.	once a day
PAC	pulmonary artery catheter
PCI	percutaneous coronary intervention
PDEI	phosphodiesterase inhibitor
PEEP	positive end-expiratory pressure
PET	positron emission tomography
pCO_2	partial pressure of carbon dioxide
PCWP	pulmonary capillary wedge pressure
pH	acid-base balance
pg	picograms
p.o.	oral
RCM	restrictive cardiomyopathy
RCTs	randomized clinical trials
RRR	relative risk reduction
RV	right ventricular
S3 gallop	diastolic heart sound
SBP	systolic blood pressure
SPECT	single photon emission tomography
STEMI	ST-segment elevation myocardial infarction
SvO_2	mixed venous oxygen saturation
t.i.d.	three times a day
TDI	tissue Doppler imaging
TOE	transoesophageal echocardiography
TR	tricuspid regurgitation
µmol	micromole
V	vasopressin receptor
VA	ventricular arrhythmia
VE/VCO_2	minute ventilation/carbon dioxide production
VHD	valvular heart disease
VO_2	oxygen consumption
VT	ventricular tachycardia
VVI pacing	right ventricular pacing

References

1. The Task Force on Heart Failure of the European Society of Cardiology. Guidelines for the diagnosis of heart failure. *Eur Heart J* 1995;**16**:741–751.
2. Task Force of the Working Group on Heart Failure of the European Society of Cardiology. The treatment of heart failure. *Eur Heart J* 1997;**18**:736–753.
3. Remme WJ, Swedberg K. Guidelines for the diagnosis and treatment of chronic heart failure. *Eur Heart J* 2001;**22**:1527–1560.
4. Nieminen MS, Bohm M, Cowie MR, Drexler H, Filippatos GS, Jondeau G, Hasin Y, Lopez-Sendon J, Mebazaa A, Metra M, Rhodes A, Swedberg K, Priori SG, Garcia MA, Blanc JJ, Budaj A, Cowie MR, Dean V, Deckers J, Burgos EF, Lekakis J, Lindahl B, Mazzotta G, Morais J, Oto A, Smiseth OA, Garcia MA, Dickstein K, Albuquerque A, Conthe P, Crespo-Leiro M, Ferrari R, Follath F, Gavazzi A, Janssens U, Komajda M, Morais J, Moreno R, Singer M, Singh S, Tendera M, Thygesen K. Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: the Task Force on Acute Heart Failure of the European Society of Cardiology. *Eur Heart J* 2005;**26**:384–416.
5. Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, Tavazzi L, Smiseth OA, Gavazzi A, Haverich A, Hoes A, Jaarsma T, Korewicki J, Levy S, Linde C, Lopez-Sendon JL, Nieminen MS, Pierard L, Remme WJ. 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. *Eur Heart J* 2005;**26**:1115–1140.
6. Poole-Wilson PA. *History, Definition and Classification of Heart Failure. Heart Failure 1* New York: Churchill Livingstone; 1997. p269–277.
7. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW, Antman EM, Smith SC Jr, Adams CD, Anderson JL, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Jacobs AK, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA 2005 Guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. *Circulation* 2005;**112**:e154–e235.
8. Heart Failure Society of America. Executive summary: HFSA 2006 Comprehensive Heart Failure Practice Guideline. *J Card Fail* 2006;**12**:10–38.
9. NICE. *Chronic Heart Failure. National Clinical Guidelines for Diagnosis and Management in Primary and Secondary Care*. The National Collaborating Centre for Chronic Conditions. London: NICE. 2005;**5**:1–163.
10. McDonagh TA, Morrison CE, Lawrence A, Ford I, Tunstall-Pedoe H, McMurray JJ, Dargie HJ. Symptomatic and asymptomatic left-ventricular systolic dysfunction in an urban population. *Lancet* 1997;**350**:829–833.
11. Wang TJ, Evans JC, Benjamin EJ, Levy D, LeRoy EC, Vasan RS. Natural history of asymptomatic left ventricular systolic dysfunction in the community. *Circulation* 2003;**108**:977–982.
12. Aurigemma GP, Gaasch WH. Clinical practice. Diastolic heart failure. *N Engl J Med* 2004;**351**:1097–1105.
13. Gaasch WH, Zile MR. Left ventricular diastolic dysfunction and diastolic heart failure. *Annu Rev Med* 2004;**55**:373–394.
14. Caruana L, Petrie MC, Davie AP, McMurray JJ. Do patients with suspected heart failure and preserved left ventricular systolic function suffer from 'diastolic heart failure' or from misdiagnosis? A prospective descriptive study. *BMJ* 2000;**321**:215–218.
15. Brutsaert DL. Diastolic heart failure: perception of the syndrome and scope of the problem. *Prog Cardiovasc Dis* 2006;**49**:153–156.
16. De Keulenaer GW, Brutsaert DL. Diastolic heart failure: a separate disease or selection bias? *Prog Cardiovasc Dis* 2007;**49**:275–283.
17. How to diagnose diastolic heart failure. European Study Group on Diastolic Heart Failure. *Eur Heart J* 1998;**19**:990–1003.
18. Brutsaert DL, De Keulenaer GW. Diastolic heart failure: a myth. *Curr Opin Cardiol* 2006;**21**:240–248.
19. McKenzie J. *Diseases of the Heart*, 3rd edn. Oxford: Oxford Medical Publications; 1913.
20. Hope JA. *Treatise on the Diseases of the Heart and Great Vessels*. London: William Kidd; 1832.
21. Heart Failure Society of America (HFSA) practice guidelines. HFSA guidelines for management of patients with heart failure caused by left ventricular systolic dysfunction—pharmacological approaches. *J Card Fail* 1999;**5**:357–382.
22. AHA medical/scientific statement. 1994 revisions to classification of functional capacity and objective assessment of patients with diseases of the heart. *Circulation* 1994;**90**:644–645.
23. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. *N Engl J Med* 1971;**285**:1441–1446.
24. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. *Heart* 2007;**93**:1137–1146.
25. Levy D, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KK, Murabito JM, Vasan RS. Long-term trends in the incidence of and survival with heart failure. *N Engl J Med* 2002;**347**:1397–1402.
26. Cowie MR, Mosterd A, Wood DA, Deckers JW, Poole-Wilson PA, Sutton GC, Grobbee DE. The epidemiology of heart failure. *Eur Heart J* 1997;**18**:208–225.
27. Cowie MR, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA, Suresh V, Sutton GC. Incidence and aetiology of heart failure; a population-based study. *Eur Heart J* 1999;**20**:421–428.
28. Murdoch DR, Love MP, Robb SD, McDonagh TA, Davie AP, Ford I, Capewell S, Morrison CE, McMurray JJ. Importance of heart failure as a cause of death. Changing contribution to overall mortality and coronary heart disease mortality in Scotland 1979–1992. *Eur Heart J* 1998;**19**:1829–1835.
29. Senni M, Tribouilloy CM, Rodeheffer RJ, Jacobsen SJ, Evans JM, Bailey KR, Redfield MM. Congestive heart failure in the community: trends in incidence and survival in a 10-year period. *Arch Intern Med* 1999;**159**:29–34.
30. MacIntyre K, Capewell S, Stewart S, Chalmers JW, Boyd J, Finlayson A, Redpath A, Pell JP, McMurray JJ. Evidence of improving prognosis in heart failure: trends in case fatality in 66 547 patients hospitalized between 1986 and 1995. *Circulation* 2000;**102**:1126–1131.
31. Blackledge HM, Tomlinson J, Squire IB. Prognosis for patients newly admitted to hospital with heart failure: survival trends in 12 220 index admissions in Leicestershire 1993–2001. *Heart* 2003;**89**:615–620.
32. Schaufelberger M, Swedberg K, Koster M, Rosen M, Rosengren A. Decreasing one-year mortality and hospitalization rates for heart failure in Sweden; data from the Swedish Hospital Discharge Registry 1988 to 2000. *Eur Heart J* 2004;**25**:300–307.
33. Stewart S, Jenkins A, Buchan S, McGuire A, Capewell S, McMurray JJ. The current cost of heart failure to the National Health Service in the UK. *Eur J Heart Fail* 2002;**4**:361–371.
34. Stewart S, MacIntyre K, Hole DJ, Capewell S, McMurray JJ. More 'malignant' than cancer? Five-year survival following a first admission for heart failure. *Eur J Heart Fail* 2001;**3**:315–322.
35. Cowie MR, Wood DA, Coats AJ, Thompson SG, Suresh V, Poole-Wilson PA, Sutton GC. Survival of patients with a new diagnosis of heart failure: a population based study. *Heart* 2000;**83**:505–510.
36. Remes J, Miettinen H, Reunanen A, Pyorala K. Validity of clinical diagnosis of heart failure in primary health care. *Eur Heart J* 1991;**12**:315–321.
37. Wheeldon NM, MacDonald TM, Flucker CJ, McKendrick AD, McDevitt DG, Struthers AD. Echocardiography in chronic heart failure in the community. *Q J Med* 1993;**86**:17–23.
38. Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, Gong Y, Liu PP. Outcome of heart failure with preserved ejection fraction in a population-based study. *N Engl J Med* 2006;**355**:260–269.
39. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med* 2006;**355**:251–259.
40. Fox KF, Cowie MR, Wood DA, Coats AJ, Gibbs JS, Underwood SR. Coronary artery disease as the cause of incident heart failure in the population. *Eur Heart J* 2001;**22**:228–236.
41. Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, Dubourg O, Kuhl U, Maisch B, McKenna WJ, Monserrat L, Pankuweit S, Rapezzi C, Seferovic P, Tavazzi L, Keren A. Classification of the cardiomyopathies: a position statement from the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2008;**29**:270–276.
42. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, Moss AJ, Seidman CE, Young JB. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. *Circulation* 2006;**113**:1807–1816.
43. Lewis T. *Diseases of the Heart*. London: MacMillan; 1933.
44. Rector TS, Cohn JN. Assessment of patient outcome with the Minnesota Living with Heart Failure questionnaire: reliability and validity during a randomized, double-blind, placebo-controlled trial of pimobendan. Pimobendan Multicenter Research Group. *Am Heart J* 1992;**124**:1017–1025.
45. McHorney CA, Ware JE Jr., Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care* 1993;**31**:247–263.

46. Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. *J Am Coll Cardiol* 2000;**35**:1245–1255.
47. Folland ED, Kriegel BJ, Henderson WG, Hammermeister KE, Sethi GK. Implications of third heart sounds in patients with valvular heart disease. The Veterans Affairs Cooperative Study on Valvular Heart Disease. *N Engl J Med* 1992;**327**:458–462.
48. Ishmail AA, Wing S, Ferguson J, Hutchinson TA, Magder S, Flegel KM. Interobserver agreement by auscultation in the presence of a third heart sound in patients with congestive heart failure. *Chest* 1987;**91**:870–873.
49. Stevenson LW, Perloff JK. The limited reliability of physical signs for estimating hemodynamics in chronic heart failure. *JAMA* 1989;**261**:884–888.
50. Spiteri MA, Cook DG, Clarke SW. Reliability of eliciting physical signs in examination of the chest. *Lancet* 1988;**1**:873–875.
51. Drazner MH, Rame JE, Stevenson LW, Dries DL. Prognostic importance of elevated jugular venous pressure and a third heart sound in patients with heart failure. *N Engl J Med* 2001;**345**:574–581.
52. Poole-Wilson PA. Relation of pathophysiologic mechanisms to outcome in heart failure. *J Am Coll Cardiol* 1993;**22**(4 Suppl A):22A–29A.
53. Lipkin DP, Canepa-Anson R, Stephens MR, Poole-Wilson PA. Factors determining symptoms in heart failure: comparison of fast and slow exercise tests. *Br Heart J* 1986;**55**:439–445.
54. Clark AL, Poole-Wilson PA, Coats AJ. Exercise limitation in chronic heart failure: central role of the periphery. *J Am Coll Cardiol* 1996;**28**:1092–1102.
55. Wilson JR, Mancini DM, Dunkman WB. Exertional fatigue due to skeletal muscle dysfunction in patients with heart failure. *Circulation* 1993;**87**:470–475.
56. Poole-Wilson PA, Ferrari R. Role of skeletal muscle in the syndrome of chronic heart failure. *Journal of molecular and cellular cardiology* 1996;**28**:2275–2285.
57. Killip T 3rd, Kimball JT. Treatment of myocardial infarction in a coronary care unit. A two year experience with 250 patients. *Am J Cardiol* 1967;**20**:457–464.
58. Forrester JS, Diamond GA, Swan HJ. Correlative classification of clinical and hemodynamic function after acute myocardial infarction. *Am J Cardiol* 1977;**39**:137–145.
59. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, Omland T, Storrow AB, Abraham WT, Wu AH, Clopton P, Steg PG, Westheim A, Knudsen CW, Perez A, Kazanegra R, Herrmann HC, McCullough PA. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med* 2002;**347**:161–167.
60. Mueller C, Laule-Kilian K, Scholer A, Frana B, Rodriguez D, Schindler C, Marsch S, Perruchoud AP. Use of B-type natriuretic peptide for the management of women with dyspnea. *Am J Cardiol* 2004;**94**:1510–1514.
61. Jourdain P, Jondeau G, Funck F, Gueffet P, Le Helloco A, Donal E, Aupetit JF, Aumont MC, Galinier M, Eicher JC, Cohen-Solal A, Juilliere Y. Plasma brain natriuretic peptide-guided therapy to improve outcome in heart failure: the STARS-BNP Multicenter Study. *J Am Coll Cardiol* 2007;**49**:1733–1739.
62. Troughton RW, Frampton CM, Yandle TG, Espiner EA, Nicholls MG, Richards AM. Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. *Lancet* 2000;**355**:1126–1130.
63. Metra M, Nodari S, Parrinello G, Specchia C, Brentana L, Rocca P, Fracassi F, Bordonali T, Milani P, Danesi R, Verzura G, Chiari E, Dei Cas L. The role of plasma biomarkers in acute heart failure. Serial changes and independent prognostic value of NT-proBNP and cardiac troponin-T. *Eur J Heart Fail* 2007;**9**:776–786.
64. Paulus WJ, Tschope C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, Marino P, Smiseth OA, De Keulenaer G, Leite-Moreira AF, Borbely A, Edes I, Handoko ML, Heymans S, Pezzali N, Pieske B, Dickstein K, Fraser AG, Brutsaert DL. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J* 2007;**28**:2539–2550.
65. Pennell DJ, Sechtem UP, Higgins CB, Manning WJ, Pohost GM, Rademakers FE, van Rossum AC, Shaw LJ, Yucel EK. Clinical indications for cardiovascular magnetic resonance (CMR): Consensus Panel report. *J Cardiovasc Magn Reson* 2004;**6**:727–765.
66. Hendel RC, Patel MR, Kramer CM, Poon M, Hendel RC, Carr JC, Gerstad NA, Gillam LD, Hodgson JM, Kim RJ, Kramer CM, Lesser JR, Martin ET, Messer JV, Redberg RF, Rubin GD, Rumsfeld JS, Taylor AJ, Weigold WG, Woodard PK, Brindis RG, Hendel RC, Douglas PS, Peterson ED, Wolk MJ, Allen JM, Patel MR. ACCF/ACR/SCCT/SCMR/ASNC/NASCI/SCAI/SIR 2006 appropriateness criteria for cardiac computed tomography and cardiac magnetic resonance imaging: a report of the American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria Working Group, American College of Radiology, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, American Society of Nuclear Cardiology, North American Society for Cardiac Imaging, Society for Cardiovascular Angiography and Interventions, and Society of Interventional Radiology. *J Am Coll Cardiol* 2006;**48**:1475–1497.
67. Cooper LT, Baughman KL, Feldman AM, Frustaci A, Jessup M, Kuhl U, Levine GN, Narula J, Starling RC, Towbin J, Virmani R. The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology Endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology. *Eur Heart J* 2007;**28**:3076–3093.
68. Jaarsma T, Strömberg A, Mårtensson J, Dracup K. Development and testing of the European Heart Failure Self-Care Behaviour Scale. *Eur J Heart Fail* 2003;**5**:363–370.
69. Granger BB, Swedberg K, Ekman I, Granger CB, Olofsson B, McMurray JJ, Yusuf S, Michelson EL, Pfeffer MA. Adherence to candesartan and placebo and outcomes in chronic heart failure in the CHARM programme: double-blind, randomised, controlled clinical trial. *Lancet* 2005;**366**:2005–2011.
70. Evangelista LS, Dracup K. A closer look at compliance research in heart failure patients in the last decade. *Prog Cardiovasc Nurs* 2000;**15**:97–103.
71. van der Wal MH, Jaarsma T, van Veldhuisen DJ. Non-compliance in patients with heart failure; how can we manage it? *Eur J Heart Fail* 2005;**7**:5–17.
72. Lainscak M, Cleland J, Lenzen MJ. Recall of lifestyle advice in patients recently hospitalised with heart failure: a EuroHeart Failure Survey analysis. *Eur J Heart Fail* 2007;**9**:1095–1103.
73. Sabate E. *Adherence to Long-term Therapies. Evidence for Action*. Geneva: WHO; 2003.
74. Stromberg A. The crucial role of patient education in heart failure. *Eur J Heart Fail* 2005;**7**:363–369.
75. Patel H, Shafazand M, Schaufelberger M, Ekman I. Reasons for seeking acute care in chronic heart failure. *Eur J Heart Fail* 2007;**9**:702–708.
76. Ekman I, Cleland JG, Swedberg K, Charlesworth A, Metra M, Poole-Wilson PA. Symptoms in patients with heart failure are prognostic predictors: insights from COMET. *J Card Fail* 2005;**11**:288–292.
77. Lewin J, Ledwidge M, O'Loughlin C, McNally C, McDonald K. Clinical deterioration in established heart failure: what is the value of BNP and weight gain in aiding diagnosis? *Eur J Heart Fail* 2005;**7**:953–957.
78. Travers B, O'Loughlin C, Murphy NF, Ryder M, Conlon C, Ledwidge M, McDonald K. Fluid restriction in the management of decompensated heart failure: no impact on time to clinical stability. *J Card Fail* 2007;**13**:128–132.
79. Nicolas JM, Fernandez-Sola J, Estruch R, Pare JC, Sacanella E, Urbano-Marquez A, Rubin E. The effect of controlled drinking in alcoholic cardiomyopathy. *Ann Intern Med* 2002;**136**:192–200.
80. Anker SD, Negassa A, Coats AJ, Afzal R, Poole-Wilson PA, Cohn JN, Yusuf S. Prognostic importance of weight loss in chronic heart failure and the effect of treatment with angiotensin-converting-enzyme inhibitors: an observational study. *Lancet* 2003;**361**:1077–1083.
81. Anker SD, Ponikowski P, Varney S, Chua TP, Clark AL, Webb-Peploe KM, Harrington D, Kox WJ, Poole-Wilson PA, Coats AJ. Wasting as independent risk factor for mortality in chronic heart failure. *Lancet* 1997;**349**:1050–1053.
82. Evangelista LS, Doering LV, Dracup K. Usefulness of a history of tobacco and alcohol use in predicting multiple heart failure readmissions among veterans. *Am J Cardiol* 2000;**86**:1339–1342.
83. Suskin N, Sheth T, Negassa A, Yusuf S. Relationship of current and past smoking to mortality and morbidity in patients with left ventricular dysfunction. *J Am Coll Cardiol* 2001;**37**:1677–1682.
84. Nichol KL, Nordin J, Mullooly J, Lask R, Fillbrandt K, Iwane M. Influenza vaccination and reduction in hospitalizations for cardiac disease and stroke among the elderly. *N Engl J Med* 2003;**348**:1322–1332.
85. Graham I, Atar D, Borch-Johnsen K, Boysen G, Burell G, Cifkova R, Dallongeville J, De Backer G, Ebrahim S, Gjelsvik B, Herrmann-Lingen C, Hoes A, Humphries S, Knapton M, Perk J, Priori SG, Pyorala K, Reiner Z, Ruilope L, Sans-Menendez S, Scholte op Reimer W, Weissberg P, Wood D, Yarnell J, Zamorano JL, Walma E, Fitzgerald T, Cooney MT, Dudina A, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Funck-Brentano C, Filippatos G, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Hellemans I, Altiner A, Bonora E, Durrington PN, Fagard R, Giampaoli S, Hemingway H, Hakansson J, Kjeldsen SE, Larsen ML, Mancia G, Manolis AJ, Orth-Gomer K, Pedersen T, Rayner M, Ryden L, Sammut M, Schneiderman N, Stalenhoef AF, Tokgozoglu L, Wiklund O, Zampelas A. European guidelines on cardiovascular disease prevention in clinical practice: executive summary. *Eur Heart J* 2007;**28**:2375–2414.
86. Piepoli MF, Flather M, Coats AJ. Overview of studies of exercise training in chronic heart failure: the need for a prospective randomized multicentre European trial. *Eur Heart J* 1998;**19**:830–841.

87. Smart N, Marwick TH. Exercise training for patients with heart failure: a systematic review of factors that improve mortality and morbidity. *Am J Med* 2004;**116**:693–706.
88. Recommendations for exercise training in chronic heart failure patients. *Eur Heart J* 2001;**22**:125–135.
89. Piepoli MF, Davos C, Francis DP, Coats AJ. Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). *BMJ* 2004;**328**:189.
90. Rees K, Taylor RS, Singh S, Coats AJ, Ebrahim S. Exercise based rehabilitation for heart failure. *Cochrane Database Syst Rev* 2004;(3):CD003331.
91. Kostis JB, Jackson G, Rosen R, Barrett-Connor E, Billups K, Burnett AL, Carson CR, Cheitlin M, DeBusk RF, Fonseca V, Ganz P, Goldstein I, Guay A, Hatzichristou D, Hollander JE, Hutter A, Katz SD, Kloner RA, Mittleman M, Montorsi F, Montorsi P, Nehra A, Sadovsky R, Shabsigh R. Sexual dysfunction and cardiac risk (the Second Princeton Consensus Conference). *Am J Cardiol* 2005;**26**:85M–93M.
92. Corra U, Pistono M, Mezzani A, Braghiroli A, Giordano A, Lanfranchi P, Bosimini E, Gnemmi M, Giannuzzi P. Sleep and exertional periodic breathing in chronic heart failure: prognostic importance and interdependence. *Circulation* 2006;**113**:44–50.
93. Naughton MT. The link between obstructive sleep apnea and heart failure: underappreciated opportunity for treatment. *Curr Cardiol Rep* 2005;**7**:211–215.
94. Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. *J Am Coll Cardiol* 2006;**48**:1527–1537.
95. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. *N Engl J Med* 1987;**316**:1429–1435.
96. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. *N Engl J Med* 1991;**325**:293–302.
97. McAlister FA, Stewart S, Ferrua S, McMurray JJ. Multidisciplinary strategies for the management of heart failure patients at high risk for admission: a systematic review of randomized trials. *J Am Coll Cardiol* 2004;**44**:810–819.
98. Packer M, Poole-Wilson PA, Armstrong PW, Cleland JG, Horowitz JD, Massie BM, Ryden L, Thygesen K, Uretsky BF. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. *Circulation* 1999; **100**:2312–2318.
99. McMurray J, Cohen-Solal A, Dietz R, Eichhorn E, Erhardt L, Hobbs R, Maggioni A, Pina I, Soler-Soler J, Swedberg K. Practical recommendations for the use of ACE inhibitors, beta-blockers, aldosterone antagonists and angiotensin receptor blockers in heart failure: putting guidelines into practice. *Eur J Heart Fail* 2005;**17**:710–721.
100. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999;**353**:9–13.
101. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999;**353**:2001–2007.
102. Hjalmarson A, Goldstein S, Fagerberg B, Wedel H, Waagstein F, Kjekshus J, Wikstrand J, El Allaf D, Vitovec J, Aldershvile J, Halinen M, Dietz R, Neuhaus KL, Janosi A, Thorgeirsson G, Dunselman PH, Gullestad L, Kuch J, Herlitz J, Rickenbacher P, Ball S, Gottlieb S, Deedwania P. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group. *JAMA* 2000;**283**:1295–1302.
103. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Castaigne A, Roecker EB, Schultz MK, DeMets DL. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001; **344**: 1651–1658.
104. Packer M, Fowler MB, Roecker EB, Coats AJ, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Staiger C, Holcslaw TL, Amann-Zalan I, DeMets DL. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. *Circulation* 2002;**106**:2194–2199.
105. Flather MD, Shibata MC, Coats AJ, Van Veldhuisen DJ, Parkhomenko A, Borbola J, Cohen-Solal A, Dumitrascu D, Ferrari R, Lechat P, Soler-Soler J, Tavazzi L, Spinarova L, Toman J, Bohm M, Anker SD, Thompson SG, Poole-Wilson PA. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J* 2005;**26**:215–225.
106. The Beta-Blocker Evaluation of Survival Trial Investigators. A trial of the beta-blocker bucindolol in patients with advanced CHF. *N Engl J Med* 2001;**344**: 1659–1667.
107. Poole-Wilson PA, Swedberg K, Cleland JG, Di Lenarda A, Hanrath P, Komajda M, Lubsen J, Lutiger B, Metra M, Remme WJ, Torp-Pedersen C, Scherhag A, Skene A. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. *Lancet* 2003;**362**:7–13.
108. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999;**341**:709–717.
109. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;**348**:1309–1321.
110. Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, Redelmeier DA. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med* 2004;**351**:543–551.
111. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001;**345**:1667–1675.
112. McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, Olofsson B, Yusuf S, Pfeffer MA. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet* 2003;**362**:767–771.
113. Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B, Ostergren J, Pfeffer MA, Swedberg K. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet* 2003;**362**:772–776.
114. Pfeffer MA, McMurray JJ, Velazquez EJ, Rouleau JL, Kober L, Maggioni AP, Solomon SD, Swedberg K, Van de Werf F, White H, Leimberger JD, Henis M, Edwards S, Zelenkofske S, Sellers MA, Califf RM. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003;**349**:1893–1906.
115. Dickstein K, Kjekshus J. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan. *Lancet* 2002;**360**:752–760.
116. McMurray JJ, Pfeffer MA, Swedberg K, Dzau VJ. Which inhibitor of the renin–angiotensin system should be used in chronic heart failure and acute myocardial infarction? *Circulation* 2004;**110**:3281–3288.
117. Cohn JN, Johnson G, Ziesche S, Cobb F, Francis G, Tristani F, Smith R, Dunkman WB, Loeb H, Wong M *et al.* A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 1991;**325**:303–310.
118. Taylor AL, Ziesche S, Yancy C, Carson P, D'Agostino R Jr., Ferdinand K, Taylor M, Adams K, Sabolinski M, Worcel M, Cohn JN. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med* 2004;**351**: 2049–2057.
119. Loeb HS, Johnson G, Henrick A, Smith R, Wilson J, Cremo R, Cohn JN. Effect of enalapril, hydralazine plus isosorbide dinitrate, and prazosin on hospitalization in patients with chronic congestive heart failure. The V-HeFT VA Cooperative Studies Group. *Circulation* 1993;**87**(6 Suppl):VI78–VI87.
120. The effect of digoxin on mortality and morbidity in patients with heart failure. The Digitalis Investigation Group. *N Engl J Med* 1997;**336**:525–533.
121. Hood WB Jr., Dans AL, Guyatt GH, Jaeschke R, McMurray JJ. Digitalis for treatment of congestive heart failure in patients in sinus rhythm: a systematic review and meta-analysis. *J Card Fail* 2004;**10**:155–164.
122. Lader E, Egan D, Hunsberger S, Garg R, Czajkowski S, McSherry F. The effect of digoxin on the quality of life in patients with heart failure. *J Card Fail* 2003;**9**: 4–12.
123. Faris R, Flather M, Purcell H, Henein M, Poole-Wilson P, Coats A. Current evidence supporting the role of diuretics in heart failure: a meta analysis of randomised controlled trials. *Int J Cardiol* 2002;**82**:149–158.
124. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation-executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients with Atrial Fibrillation). *Eur Heart J* 2006;**27**:1979–2030.
125. Cleland JG, Findlay I, Jafri S, Sutton G, Falk R, Bulpitt C, Prentice C, Ford I, Trainer A, Poole-Wilson PA. The Warfarin/Aspirin Study in Heart failure (WASH): a randomized trial comparing antithrombotic strategies for patients with heart failure. *Am Heart J* 2004;**148**:157–164.

126. Cleland JG, Ghosh J, Freemantle N, Kaye GC, Nasir M, Clark AL, Coletta AP. Clinical trials update and cumulative meta-analyses from the American College of Cardiology: WATCH, SCD-HeFT, DINAMIT, CASINO, INSPIRE, STRATUS-US, RIO-lipids and cardiac resynchronisation therapy in heart failure. *Eur J Heart Fail* 2004;**6**:501–508.
127. Kjekshus J, Apetrei E, Barrios V, Bohm M, Cleland JG, Cornel JH, Dunselman P, Fonseca C, Goudev A, Grande P, Gullestad L, Hjalmarson A, Hradec J, Janosi A, Kamensky G, Komajda M, Korewicki J, Kuusi T, Mach F, Mareev V, McMurray JJ, Ranjith N, Schaufelberger M, Vanhaecke J, van Veldhuisen DJ, Waagstein F, Wedel H, Wikstrand J. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med* 2007;**357**:2248–2261.
128. Setaro JF, Zaret BL, Schulman DS, Black HR, Soufer R. Usefulness of verapamil for congestive heart failure associated with abnormal left ventricular diastolic filling and normal left ventricular systolic performance. *Am J Cardiol* 1990;**66**:981–986.
129. Hung MJ, Cherng WJ, Kuo LT, Wang CH. Effect of verapamil in elderly patients with left ventricular diastolic dysfunction as a cause of congestive heart failure. *Int J Clin Pract* 2002;**56**:57–62.
130. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet* 2003;**362**:777–781.
131. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *Eur Heart J* 2006;**27**:2338–2345.
132. Lloyd-Jones DM, Larson MG, Leip EP, Beiser A, D'Agostino RB, Kannel WB, Murabito JM, Vasan RS, Benjamin EJ, Levy D. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. *Circulation* 2002;**106**:3068–3072.
133. Gheorghiade M, Sopko G, De Luca L, Velazquez EJ, Parker JD, Binkley PF, Sadowski Z, Golba KS, Prior DL, Rouleau JL, Bonow RO. Navigating the crossroads of coronary artery disease and heart failure. *Circulation* 2006;**114**:1202–1213.
134. Shanmugan G, Légaré JF. Revascularization for ischemic cardiomyopathy. *Curr Opin Cardiol* 2008;**23**:148–152.
135. Schinkel AF, Poldermans D, Elhendy A, Bax JJ. Assessment of myocardial viability in patients with heart failure. *J Nucl Med* 2007;**48**:1135–1146.
136. Vahanian A, Baumgartner H, Bax J, Butchart E, Dion R, Filippatos G, Flachskampf F, Hall R, Iung B, Kasprzak J, Nataf P, Tornos P, Torracca L, Wenink A. Guidelines on the management of valvular heart disease: The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. *Eur Heart J* 2007;**28**:230–268.
137. Pereira JJ, Lauer MS, Bashir M, Afridi I, Blackstone EH, Stewart WJ, McCarthy PM, Thomas JD, Asher CR. Survival after aortic valve replacement for severe aortic stenosis with low transvalvular gradients and severe left ventricular dysfunction. *J Am Coll Cardiol* 2002;**9**:1356–1363.
138. Vardas PE, Auricchio A, Blanc JJ, Daubert JC, Drexler H, Ector H, Gasparini M, Linde C, Morgado FB, Oto A, Sutton R, Trusz-Gluza M. Guidelines for cardiac pacing and cardiac resynchronization therapy: the task force for cardiac pacing and cardiac resynchronization therapy of the European Society of Cardiology. Developed in collaboration with the European Heart Rhythm Association. *Eur Heart J* 2007;**28**:2256–2295.
139. Anderson L, Miyazaki C, Sutherland G, Oh J. Patient selection and echocardiographic assessment of dyssynchrony in cardiac resynchronization therapy. *Circulation* 2008;**117**:2009–2023.
140. Chung ES, Leon AR, Tavazzi L, Sun JP, Nihoyannopoulos P, Merlino J, Abraham WT, Ghio S, Leclercq C, Bax JJ, Yu CM, Gorcsan J 3rd, St John Sutton M, De Sutter J, Murillo J. Results of the Predictors of Response to CRT (PROSPECT) trial. *Circulation* 2008;**117**:2608–2616.
141. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavell AL, Hayes DL, Ellestad M, Trupp RJ, Underwood J, Pickering F, Truex C, McAtee P, Messenger J. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;**346**:1845–1853.
142. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;**350**:2140–2150.
143. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;**352**:1539–1549.
144. Rivero-Ayerza M, Theuns DA, Garcia-Garcia HM, Boersma E, Simoons M, Jordaens LJ. Effects of cardiac resynchronization therapy on overall mortality and mode of death: a meta-analysis of randomized controlled trials. *Eur Heart J* 2006;**27**:2682–2688.
145. Fruhwald FM, Fahrleitner-Pammer A, Berger R, Leyva F, Freemantle N, Erdmann E, Gras D, Kappenberger L, Tavazzi L, Daubert JC, Cleland JG. Early and sustained effects of cardiac resynchronization therapy on N-terminal pro-B-type natriuretic peptide in patients with moderate to severe heart failure and cardiac dyssynchrony. *Eur Heart J* 2007;**28**:1592–1597.
146. Siebels J, Kuck KH. Implantable cardioverter defibrillator compared with antiarrhythmic drug treatment in cardiac arrest survivors (the Cardiac Arrest Study Hamburg). *Am Heart J* 1994;**127**:1139–1144.
147. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. *N Engl J Med* 1997;**337**:1576–1583.
148. Connolly SJ, Gent M, Roberts RS, Dorian P, Roy D, Sheldon RS, Mitchell LB, Green MS, Klein GJ, O'Brien B. Canadian implantable defibrillator study (CIDS): a randomized trial of the implantable cardioverter defibrillator against amiodarone. *Circulation* 2000;**101**:1297–1302.
149. Connolly SJ, Hallstrom AP, Cappato R, Schron EB, Kuck KH, Zipes DP, Greene HL, Boczor S, Domanski M, Follmann D, Gent M, Roberts RS. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. AVID, CASH and CIDS studies. Antiarrhythmics vs Implantable Defibrillator study. Cardiac Arrest Study Hamburg. Canadian Implantable Defibrillator Study. *Eur Heart J* 2000;**21**:2071–2078.
150. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med* 1989;**321**:406–412.
151. Julian DG, Camm AJ, Frangin G, Janse MJ, Munoz A, Schwartz PJ, Simon P. Randomised trial of effect of amiodarone on mortality in patients with left-ventricular dysfunction after recent myocardial infarction: EMIAT. European Myocardial Infarct Amiodarone Trial Investigators. *Lancet* 1997;**349**:667–674.
152. Cairns JA, Connolly SJ, Roberts R, Gent M. Randomised trial of outcome after myocardial infarction in patients with frequent or repetitive ventricular premature depolarisations: CAMIAT. Canadian Amiodarone Myocardial Infarction Arrhythmia Trial Investigators. *Lancet* 1997;**349**:675–682.
153. Singh SN, Fletcher RD, Fisher SG, Singh BN, Lewis HD, Deedwania PC, Massie BM, Colling C, Lazzeri D. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure. *N Engl J Med* 1995;**333**:77–82.
154. Waldo AL, Camm AJ, deRuyter H, Friedman PL, MacNeil DJ, Pauls JF, Pitt B, Pratt CM, Schwartz PJ, Veltri EP. Effect of d-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. The SWORD Investigators. Survival With Oral d-Sotalol. *Lancet* 1996;**348**:7–12.
155. Torp-Pedersen C, Moller M, Bloch-Thomsen PE, Kober L, Sandoe E, Egstrup K, Agner E, Carlsen J, Videbaek J, Marchant B, Camm AJ. Dofetilide in patients with congestive heart failure and left ventricular dysfunction. Danish Investigations of Arrhythmia and Mortality on Dofetilide Study Group. *N Engl J Med* 1999;**341**:857–865.
156. Camm AJ, Pratt CM, Schwartz PJ, Al-Khalidi HR, Spyt MJ, Holroyde MJ, Karam R, Sonnenblick EH, Brum JM. Mortality in patients after a recent myocardial infarction: a randomized, placebo-controlled trial of azimilide using heart rate variability for risk stratification. *Circulation* 2004;**109**:990–996.
157. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH. Amiodarone or an implantable cardioverter–defibrillator for congestive heart failure. *N Engl J Med* 2005;**352**:225–237.
158. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, Levine JH, Saksena S, Waldo AL, Wilber D, Brown MW, Heo M. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. *N Engl J Med* 1996;**335**:1933–1940.
159. Bigger JT Jr. Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary-artery bypass graft surgery. Coronary Artery Bypass Graft (CABG) Patch Trial Investigators. *N Engl J Med* 1997;**337**:1569–1575.
160. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. *N Engl J Med* 1999;**341**:1882–1890.
161. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;**346**:877–883.
162. Hohnloser SH, Kuck KH, Dorian P, Roberts RS, Hampton JR, Hatala R, Fain E, Gent M, Connolly SJ. Prophylactic use of an implantable cardioverter–defibrillator after acute myocardial infarction. *N Engl J Med* 2004;**351**:2481–2488.

163. Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, Gregoratos G, Klein G, Moss AJ, Myerburg RJ, Priori SG, Quinones MA, Roden DM, Silka MJ, Tracy C, Blanc JJ, Budaj A, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo JL, Zamorano JL, Smith SC Jr, Jacobs AK, Adams CD, Antman EM, Anderson JL, Hunt SA, Halperin JL, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death—executive summary: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death) Developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Eur Heart J* 2006;**27**:2099–2140.
164. Bansch D, Antz M, Boczor S, Volkmer M, Tebbenjohanns J, Seidl K, Block M, Gietzen F, Berger J, Kuck KH. Primary prevention of sudden cardiac death in idiopathic dilated cardiomyopathy: the Cardiomyopathy Trial (CAT). *Circulation* 2002;**105**:1453–1458.
165. Strickberger SA, Hummel JD, Bartlett TG, Frumin HI, Schuger CD, Beau SL, Bitar C, Morady F. Amiodarone versus implantable cardioverter–defibrillator:-randomized trial in patients with nonischemic dilated cardiomyopathy and asymptomatic nonsustained ventricular tachycardia—AMIOVIRT. *J Am Coll Cardiol* 2003;**41**:1707–1712.
166. Kadish A, Dyer A, Daubert JP, Quigg R, Estes NA, Anderson KP, Calkins H, Hoch D, Goldberger J, Shalaby A, Sanders WE, Schaechter A, Levine JH. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. *N Engl J Med* 2004;**350**:2151–2158.
167. Desai AS, Fang JC, Maisel WH, Baughman KL. Implantable defibrillators for the prevention of mortality in patients with nonischemic cardiomyopathy: a meta-analysis of randomized controlled trials. *JAMA* 2004;**292**:2874–2879.
168. Miller LW, Pagani FD, Russell SD, John R, Boyle AJ, Aaronson KD, Conte JV, Naka Y, Mancini D, Delgado RM, MacGillivray TE, Farrar DJ, Frazier OH. Use of a continuous-flow device in patients awaiting heart transplantation. *N Engl J Med* 2007;**357**:885–896.
169. Stevenson LW, Shekar P. Ventricular assist devices for durable support. *Circulation* 2005;**112**:e111–e115.
170. Costanzo MR, Guglin ME, Saltzberg MT, Jessup ML, Bart BA, Teerlink JR, Jaski BE, Fang JC, Feller ED, Haas GJ, Anderson AS, Schollmeyer MP, Sobotka PA. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J Am Coll Cardiol* 2007;**49**:675–683.
171. Efremidis M, Pappas L, Sideris A, Filippatos G. Management of atrial fibrillation in patients with heart failure. *J CardFail* 2008;**14**:232–237.
172. Roy D, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, Bourassa MG, Arnold JM, Buxton AE, Camm AJ, Connolly SJ, Dubuc M, Ducharme A, Guerra PG, Hohnloser SH, Lambert J, Le Heuzey JY, O'Hara G, Pedersen OD, Rouleau JL, Singh BN, Stevenson LW, Stevenson WG, Thibault B, Waldo AL. Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med* 2008;**358**:2667–2677.
173. Carbucicchio C, Santamaria M, Trevisi N, Maccabelli G, Giraldi F, Fassini G, Riva S, Moltrasio M, Cireddu M, Veglia F, Della Bella P. Catheter ablation for the treatment of electrical storm in patients with implantable cardioverter–defibrillators: short- and long-term outcomes in a prospective single-center study. *Circulation* 2008;**117**:462–469.
174. Naegeli B, Kurz DJ, Koller D, Straumann E, Furrer M, Maurer D, Minder E, Bertel O. Single-chamber ventricular pacing increases markers of left ventricular dysfunction compared with dual-chamber pacing. *Europace* 2007;**9**:194–199.
175. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, Struijker Boudier HA, Zanchetti A, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Kjeldsen SE, Erdine S, Narkiewicz K, Kiowski W, Agabiti-Rosei E, Ambrosioni E, Cifkova R, Dominiczak A, Fagard R, Heagerty AM, Laurent S, Lindholm LH, Mancia G, Manolis A, Nilsson PM, Redon J, Schmieder RE, Struijker-Boudier HA, Viigimaa M, Filippatos G, Adamopoulos S, Agabiti-Rosei E, Ambrosioni E, Bertomeu V, Clement D, Erdine S, Farsang C, Gaita D, Kiowski W, Lip G, Mallion JM, Manolis AJ, Nilsson PM, O'Brien E, Ponikowski P, Redon J, Ruschitzka F, Tamargo J, van Zwieten P, Viigimaa M, Waeber B, Williams B, Zamorano JL, The task force for the management of arterial hypertension of the European Society of H, The task force for the management of arterial hypertension of the European Society of C. 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2007;**28**:1462–1536.
176. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. *JAMA* 1996;**275**:1557–1562.
177. Nichols GA, Gullion CM, Koro CE, Ephross SA, Brown JB. The incidence of congestive heart failure in type 2 diabetes: an update. *Diabetes Care* 2004;**27**:1879–1884.
178. Macdonald MR, Petrie MC, Hawkins NM, Petrie JR, Fisher M, McKelvie R, Aguilar D, Krum H, McMurray JJV. Diabetes, left ventricular systolic dysfunction, and chronic heart failure. *Eur Heart J* 2008;**29**:1224–1240.
179. Macdonald MR, Petrie MC, Varyani F, Ostergren J, Michelson EL, Young JB, Solomon SD, Granger CB, Swedberg K, Yusuf S, Pfeffer MA, McMurray JJ. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: an analysis of the Candesartan in Heart failure: assessment of Reduction in Mortality and morbidity (CHARM) programme. *Eur Heart J* 2008;**29**:1337–1385.
180. De Groote P, Lamblin N, Mouquet F, Plichon D, McFadden E, Van Belle E, Bauters C. Impact of diabetes mellitus on long-term survival in patients with congestive heart failure. *Eur Heart J* 2004;**25**:656–662.
181. Ryden L, Standl E, Bartnik M, Van den Berghe G, Betteridge J, de Boer MJ, Cosentino F, Jonsson B, Laakso M, Malmberg K, Priori S, Ostergren J, Tuomilehto J, Thrainsdottir I, Vanhorebeek I, Stramba-Badiale M, Lindgren P, Qiao Q, Priori SG, Blanc JJ, Budaj A, Camm J, Dean V, Deckers J, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo J, Zamorano JL, Deckers JW, Bertrand M, Charbonnel B, Erdmann E, Ferrannini E, Flyvbjerg A, Gohlke H, Juanatey JR, Graham I, Monteiro PF, Parhofer K, Pyorala K, Raz I, Schernthaner G, Volpe M, Wood D. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). *Eur Heart J* 2007;**28**:88–136.
182. Smith GL, Lichtman JH, Bracken MB, Shlipak MG, Phillips CO, DiCapua P, Krumholz HM. Renal impairment and outcomes in heart failure: systematic review and meta-analysis. *J Am Coll Cardiol* 2006;**47**:1987–1996.
183. Le Jemtel TH, Padeletti M, Jelic S. Diagnostic and therapeutic challenges in patients with coexistent chronic obstructive pulmonary disease and chronic heart failure. *J Am Coll Cardiol* 2007;**49**:171–180.
184. Rutten FH, Cramer MJ, Grobbee DE, Sachs AP, Kirkels JH, Lammers JW, Hoes AW. Unrecognized heart failure in elderly patients with stable chronic obstructive pulmonary disease. *Eur Heart J* 2005;**26**:1887–1894.
185. Rutten FH, Cramer MJ, Lammers JW, Grobbee DE, Hoes AW. Heart failure and chronic obstructive pulmonary disease: an ignored combination? *Eur J Heart Fail* 2006;**8**:706–711.
186. Sin DD, Man SF. Chronic obstructive pulmonary disease as a risk factor for cardiovascular morbidity and mortality. *Proc Am Thorac Soc* 2005;**2**:8–11.
187. Macchia A, Monte S, Romero M, D'Ettorre A, Tognoni G. The prognostic influence of chronic obstructive pulmonary disease in patients hospitalised for chronic heart failure. *Eur J Heart Fail* 2007;**9**:942–948.
188. Egred M, Shaw S, Mohammad B, Waitt P, Rodrigues E. Under-use of beta-blockers in patients with ischaemic heart disease and concomitant chronic obstructive pulmonary disease. *Q J Med* 2005;**98**:493–497.
189. Shelton RJ, Rigby AS, Cleland JG, Clark AL. Effect of a community heart failure clinic on uptake of beta blockers by patients with obstructive airways disease and heart failure. *Heart* 2006;**92**:331–336.
190. Salpeter S, Ormiston T, Salpeter E. Cardioselective beta-blockers for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2005;(4):CD003566.
191. Lopez-Sendon J, Swedberg K, McMurray J, Tamargo J, Maggioni AP, Dargie H, Tendera M, Waagstein F, Kjekshus J, Lechat P, Torp-Pedersen C. Expert consensus document on beta-adrenergic receptor blockers. *Eur Heart J* 2004;**25**:1341–1362.
192. Gosker HR, Lencer NH, Franssen FM, van der Vusse GJ, Wouters EF, Schols AM. Striking similarities in systemic factors contributing to decreased exercise capacity in patients with severe chronic heart failure or COPD. *Chest* 2003;**123**:1416–1424.
193. Felker GM, Adams KF Jr, Gattis WA, O'Connor CM. Anemia as a risk factor and therapeutic target in heart failure. *J Am Coll Cardiol* 2004;**44**:959–966.
194. Tang YD, Katz SD. Anemia in chronic heart failure: prevalence, etiology, clinical correlates, and treatment options. *Circulation* 2006;**113**:2454–2461.
195. Opasich C, Cazzola M, Scelsi L, De Feo S, Bosimini E, Lagioia R, Febo O, Ferrari R, Fucili A, Moratti R, Tramarin R, Tavazzi L. Blunted erythropoietin production and defective iron supply for erythropoiesis as major causes of anaemia in patients with chronic heart failure. *Eur Heart J* 2005;**26**:2232–2237.
196. Nanas JN, Matsouka C, Karageorgopoulos D, Leonti A, Tsolakis E, Drakos SG, Tsagalou EP, Maroulidis GD, Alexopoulos GP, Kanakakis JE, Anastasiou-Nana MI. Etiology of anemia in patients with advanced heart failure. *J Am Coll Cardiol* 2006;**48**:2485–2489.

197. Mancini DM, Katz SD, Lang CC, LaManca J, Hudaihed A, Androne AS. Effect of erythropoietin on exercise capacity in patients with moderate to severe chronic heart failure. *Circulation* 2003;**107**:294–299.
198. Ponikowski P, Anker SD, Szachniewicz J, Okonko D, Ledwidge M, Zymlinski R, Ryan E, Wasserman SM, Baker N, Rosser D, Rosen SD, Poole-Wilson PA, Banasiak W, Coats AJ, McDonald K. Effect of darbepoetin alfa on exercise tolerance in anemic patients with symptomatic chronic heart failure: a randomized, double-blind, placebo-controlled trial. *J Am Coll Cardiol* 2007;**49**:753–762.
199. van Veldhuisen DJ, Dickstein K, Cohen-Solal A, Lok DJ, Wasserman SM, Baker N, Rosser D, Cleland JG, Ponikowski P. Randomized, double-blind, placebo-controlled study to evaluate the effect of two dosing regimens of darbepoetin alfa in patients with heart failure and anaemia. *Eur Heart J* 2007;**28**:2208–2216.
200. Okonko DO, Grzeslo A, Witkowski T, Mandal AK, Slater RM, Roughton M, Foldes G, Thum T, Majda J, Banasiak W, Missouris CG, Poole-Wilson PA, Anker SD, Ponikowski P. Effect of intravenous iron sucrose on exercise tolerance in anemic and nonanemic patients with symptomatic chronic heart failure and iron deficiency FERRIC-HF: a randomized, controlled, observer-blinded trial. *J Am Coll Cardiol* 2008;**51**:103–112.
201. von Haehling S, Doehner W, Anker SD. Nutrition, metabolism, and the complex pathophysiology of cachexia in chronic heart failure. *Cardiovasc Res* 2007;**73**:298–309.
202. Springer J, Filippatos G, Akashi YJ, Anker SD. Prognosis and therapy approaches of cardiac cachexia. *Curr Opin Cardiol* 2006;**21**:229–233.
203. Daliento L, Somerville J, Presbitero P, Menti L, Brach-Prever S, Rizzoli G, Stone S. Eisenmenger syndrome. Factors relating to deterioration and death. *Eur Heart J* 1998;**19**:1845–1855.
204. Diller GP, Dimopoulos K, Broberg CS, Kaya MG, Naghotra US, Uebing A, Harries C, Goktekin O, Gibbs JS, Gatzoulis MA. Presentation, survival prospects, and predictors of death in Eisenmenger syndrome: a combined retrospective and case-control study. *Eur Heart J* 2006;**27**:1737–1742.
205. Filippatos G, Zannad F. An introduction to acute heart failure syndromes: definition and classification. *Heart Fail Rev* 2007;**12**:87–90.
206. Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Follath F, Harjola VP, Hochadel M, Komajda M, Lassus J, Lopez-Sendon JL, Ponikowski P, Tavazzi L. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. *Eur Heart J* 2006;**27**:2725–2736.
207. Yancy CW, Lopatin M, Stevenson LW, De Marco T, Fonarow GC. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. *J Am Coll Cardiol* 2006;**47**:76–84.
208. Gheorghiade M, Zannad F, Sopko G, Klein L, Pina IL, Konstam MA, Massie BM, Roland E, Targum S, Collins SP, Filippatos G, Tavazzi L. Acute heart failure syndromes: current state and framework for future research. *Circulation* 2005;**112**:3958–3968.
209. Tavazzi L, Maggioni AP, Lucci D, Cacciatore G, Ansalone G, Oliva F, Porcu M. Nationwide survey on acute heart failure in cardiology ward services in Italy. *Eur Heart J* 2006;**27**:1207–1215.
210. Zannad F, Mebazaa A, Juilliere Y, Cohen-Solal A, Guize L, Alla F, Rouge P, Blin P, Barlet MH, Paolozzi L, Vincent C, Desnos M, Samii K. Clinical profile, contemporary management and one-year mortality in patients with severe acute heart failure syndromes: the EFICA study. *Eur J Heart Fail* 2006;**8**:697–705.
211. Siirila-Waris K, Lassus J, Melin J, Peuhkurinen K, Nieminen MS, Harjola VP. Characteristics, outcomes, and predictors of 1-year mortality in patients hospitalized for acute heart failure. *Eur Heart J* 2006;**27**:3011–3017.
212. Fonarow GC, Adams KF Jr., Abraham WT, Yancy CW, Boscardin WJ. Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. *JAMA* 2005;**293**:572–580.
213. Maisel AS, Bhalla V, Braunwald E. Cardiac biomarkers: a contemporary status report. *Nature Clin Pract* 2006;**3**:24–34.
214. Chen AA, Wood MJ, Krauser DG, Baggish AL, Tung R, Anwaruddin S, Picard MH, Januzzi JL. NT-proBNP levels, echocardiographic findings, and outcomes in breathless patients: results from the ProBNP Investigation of Dyspnoea in the Emergency Department (PRIDE) echocardiographic substudy. *Eur Heart J* 2006;**27**:839–845.
215. Bassand JP, Hamm CW, Ardissino D, Boersma E, Budaj A, Fernandez-Aviles F, Fox KA, Hasdai D, Ohman EM, Wallentin L, Wijns W. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. *Eur Heart J* 2007;**28**:1598–1660.
216. Cleland JG, Abdellah AT, Khaleva O, Coletta AP, Clark AL. Clinical trials update from the European Society of Cardiology Congress 2007: 3CPO, ALOFT, PROSPECT and statins for heart failure. *Eur J Heart Fail* 2007;**9**:1070–1073.
217. Masip J. Non-invasive ventilation. *Heart Fail Rev* 2007;**12**:119–124.
218. Masip J, Roque M, Sanchez B, Fernandez R, Subirana M, Exposito JA. Noninvasive ventilation in acute cardiogenic pulmonary edema: systematic review and meta-analysis. *JMA* 2005;**294**:3124–3130.
219. Peter JV, Moran JL, Phillips-Hughes J, Graham P, Bersten AD. Effect of non-invasive positive pressure ventilation (NIPPV) on mortality in patients with acute cardiogenic pulmonary oedema: a meta-analysis. *Lancet* 2006;**367**:1155–1163.
220. Hoffman JR, Reynolds S. Comparison of nitroglycerin, morphine and furosemide in treatment of presumed pre-hospital pulmonary edema. *Chest* 1987;**92**:586–593.
221. Lee G, DeMaria AN, Amsterdam EA, Realyvasquez F, Angel J, Morrison S, Mason DT. Comparative effects of morphine, meperidine and pentazocine on cardiocirculatory dynamics in patients with acute myocardial infarction. *Am J Med* 1976;**60**:949–955.
222. Peacock WHJ, Diercks D, Fonorow G, Emerman C. Morphine for acute decompensated heart failure: valuable adjunct or a historical remnant? *Acad Emerg Med* 2005;**12**:97b–98b.
223. Channer KS, McLean KA, Lawson-Matthew P, Richardson M. Combination diuretic treatment in severe heart failure: a randomised controlled trial. *Br Heart J* 1994;**71**:146–150.
224. Cotter G, Metzkor E, Kaluski E, Faigenberg Z, Miller R, Simovitz A, Shaham O, Marghitay D, Koren M, Blatt A, Moshkovitz Y, Zaidenstein R, Golik A. Randomised trial of high-dose isosorbide dinitrate plus low-dose furosemide versus high-dose furosemide plus low-dose isosorbide dinitrate in severe pulmonary oedema. *Lancet* 1998;**351**:389–393.
225. Jhund PS, McMurray JJ, Davie AP. The acute vascular effects of frusemide in heart failure. *Br J Clin Pharmacol* 2000;**50**:9–13.
226. Pivac N, Rumboldt Z, Sardelic S, Bagatin J, Polic S, Ljutic D, Naranca M, Capkun V. Diuretic effects of furosemide infusion versus bolus injection in congestive heart failure. *Int J Clin Pharmacol Res* 1998;**18**:121–128.
227. Konstam MA, Gheorghiade M, Burnett JC Jr., Grinfeld L, Maggioni AP, Swedberg K, Udelson JE, Zannad F, Cook T, Ouyang J, Zimmer C, Orlandi C. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. *JAMA* 2007;**297**:1319–1331.
228. Elkayam U, Bitar F, Akhter MW, Khan S, Patrus S, Derakhshani M. Intravenous nitroglycerin in the treatment of decompensated heart failure: potential benefits and limitations. *J Cardiovasc Pharmacol Ther* 2004;**9**:227–241.
229. Moazemi K, Chana JS, Willard AM, Kocheril AG. Intravenous vasodilator therapy in congestive heart failure. *Drugs Aging* 2003;**20**:485–508.
230. Bayram M, De Luca L, Massie MB, Gheorghiade M. Reassessment of dobutamine, dopamine, and milrinone in the management of acute heart failure syndromes. *Am J Cardiol* 2005;**96**:47G–58G.
231. Felker GM, Benza RL, Chandler AB, Leimberger JD, Cuffe MS, Califf RM, Gheorghiade M, O'Connor CM. Heart failure etiology and response to milrinone in decompensated heart failure: results from the OPTIME-CHF study. *J Am Coll Cardiol* 2003;**41**:997–1003.
232. Galley HF. Renal-dose dopamine: will the message now get through? *Lancet* 2000;**356**:2112–2113.
233. Gilbert EM, Hershberger RE, Wiechmann RJ, Movsesian MA, Bristow MR. Pharmacologic and hemodynamic effects of combined beta-agonist stimulation and phosphodiesterase inhibition in the failing human heart. *Chest* 1995;**108**:1524–1532.
234. Lowes BD, Tsvetkova T, Eichhorn EJ, Gilbert EM, Bristow MR. Milrinone versus dobutamine in heart failure subjects treated chronically with carvedilol. *Int J Cardiol* 2001;**81**:141–149.
235. Mebazaa A, Nieminen MS, Packer M, Cohen-Solal A, Kleber FX, Pocock SJ, Thakkar R, Padley RJ, Poder P, Kivikko M. Levosimendan vs dobutamine for patients with acute decompensated heart failure: the SURVIVE Randomized Trial. *JAMA* 2007;**297**:1883–1891.
236. Metra M, Nodari S, D'Aloia A, Muneretto C, Robertson AD, Bristow MR, Dei Cas L. Beta-blocker therapy influences the hemodynamic response to inotropic agents in patients with heart failure: a randomized comparison of dobutamine and enoximone before and after chronic treatment with metoprolol or carvedilol. *J Am Coll Cardiol* 2002;**40**:1248–1258.
237. Cleland JG, Freemantle N, Coletta AP, Clark AL. Clinical trials update from the American Heart Association: REPAIR-AMI, ASTAMI, JELIS, MEGA, REVIVE-II, SURVIVE, and PROACTIVE. *Eur J Heart Fail* 2006;**8**:105–110.
238. Stewart S. Financial aspects of heart failure programs of care. *Eur J Heart Fail* 2005;**7**:423–428.
239. Yu DS, Thompson DR, Lee DT. Disease management programmes for older people with heart failure: crucial characteristics which improve post-discharge outcomes. *Eur Heart J* 2006;**27**:596–612.
240. de la Porte PW, Lok DJ, van Veldhuisen DJ, van Wijngaarden J, Cornel JH, Zuithoff NP, Badings E, Hoes AW. Added value of a physician- and nurse-

directed heart failure clinic: results from the Deventer–Alkmaar heart failure study. *Heart* 2007;**93**:819–825.
241. Jaarsma T, van der Wal MH, Lesman-Leegte I, Luttik ML, Hogenhuis J, Veeger NJ, Sanderman R, Hoes AW, van Gilst WH, Lok DJ, Dunselman PH, Tijssen JG, Hillege HL, van Veldhuisen DJ. Effect of moderate or intensive disease management program on outcome in patients with heart failure: Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure (COACH). *Arch Intern Med* 2008;**168**:316–324.
242. Stewart S, Marley JE, Horowitz JD. Effects of a multidisciplinary, home-based intervention on unplanned readmissions and survival among patients with chronic congestive heart failure: a randomised controlled study. *Lancet* 1999; **354**:1077–1083.
243. Stromberg A, Martensson J, Fridlund B, Levin LA, Karlsson JE, Dahlstrom U. Nurse-led heart failure clinics improve survival and self-care behaviour in patients with heart failure: results from a prospective, randomised trial. *Eur Heart J* 2003;**24**:1014–1023.
244. Blue L, McMurray J. How much responsibility should heart failure nurses take? *Eur J Heart Fail* 2005;**7**:351–361.
245. Krumholz HM, Amatruda J, Smith GL, Mattera JA, Roumanis SA, Radford MJ, Crombie P, Vaccarino V. Randomized trial of an education and support intervention to prevent readmission of patients with heart failure. *J Am Coll Cardiol* 2002; **39**:83–89.
246. Koelling TM, Johnson ML, Cody RJ, Aaronson KD. Discharge education improves clinical outcomes in patients with chronic heart failure. *Circulation* 2005;**111**:179–185.
247. Clark RA, Inglis SC, McAlister FA, Cleland JG, Stewart S. Telemonitoring or structured telephone support programmes for patients with chronic heart failure: systematic review and meta-analysis. *BMJ* 2007;**334**:942.
248. Corra U, Giannuzzi P, Adamopoulos S, Bjornstad H, Bjarnason-Weherns B, Cohen-Solal A, Dugmore D, Fioretti P, Gaita D, Hambrecht R, Hellermans I, McGee H, Mendes M, Perk J, Saner H, Vanhees L. Executive summary of the position paper of the Working Group on Cardiac Rehabilitation and Exercise Physiology of the European Society of Cardiology (ESC): core components of cardiac rehabilitation in chronic heart failure. *Eur J Cardiovasc Prev Rehabil* 2005;**12**:321–325.
249. Gohler A, Januzzi JL, Worrell SS, Osterziel KJ, Gazelle GS, Dietz R, Siebert U. A systematic meta-analysis of the efficacy and heterogeneity of disease management programs in congestive heart failure. *J Card Fail* 2006;**12**:554–567.
250. Roccaforte R, Demers C, Baldassarre F, Teo KK, Yusuf S. Effectiveness of comprehensive disease management programmes in improving clinical outcomes in heart failure patients. A meta-analysis. *Eur J Heart Fail* 2005;**7**:1133–1144.
251. Goodlin SJ, Hauptman PJ, Arnold R, Grady K, Hershberger RE, Kutner J, Masoudi F, Spertus J, Dracup K, Cleary JF, Medak R, Crispell K, Pina I, Stuart B, Whitney C, Rector T, Teno J, Renlund DG. Consensus statement: palliative and supportive care in advanced heart failure. *J Card Fail* 2004;**10**: 200–209.
252. Metra M, Ponikowski P, Dickstein K, McMurray JJ, Gavazzi A, Bergh CH, Fraser AG, Jaarsma T, Pitsis A, Mohacsi P, Bohm M, Anker S, Dargie H, Brutsaert D, Komajda M. Advanced chronic heart failure: a position statement from the Study Group on Advanced Heart Failure of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2007;**9**:684–694.