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European Journal of Heart Failure 9 (2007) 684–694

The European Journal of Heart Failure

www.elsevier.com/locate/ejheart

Review

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

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Received 28 December 2006; received in revised form 5 March 2007; accepted 18 April 2007

Abstract

Therapy has improved the survival of heart failure (HF) patients. However, many patients progress to advanced chronic HF (ACHF). We propose a practical clinical definition and describe the characteristics of this condition.

Patients that are generally recognised as ACHF often exhibit the following characteristics: 1) severe symptoms (NYHA class III to IV); 2) episodes with clinical signs of fluid retention and/or peripheral hypoperfusion; 3) objective evidence of severe cardiac dysfunction, shown by at least one of the following: left ventricular ejection fraction < 30%, pseudonormal or restrictive mitral inflow pattern at Doppler-echocardiography; high left and/or right ventricular filling pressures; elevated B-type natriuretic peptides; 4) severe impairment of functional capacity demonstrated by either inability to exercise, a 6-minute walk test distance < 300 m or a peak oxygen uptake < 12–14 ml/kg/min; 5) history of >1 HF hospitalisation in the past 6 months; 6) presence of all the previous features despite optimal therapy. This definition

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doi:10.1016/j.ejheart.2007.04.003

identifies a group of patients with compromised quality of life, poor prognosis, and a high risk of clinical events. These patients deserve effective therapeutic options and should be potential targets for future clinical research initiatives.

Keywords: Heart failure; Prognosis; Treatment

1. Introduction: changing clinical characteristics of heart failure

Untreated heart failure (HF) is usually a progressive syndrome, characterised by worsening of symptoms, unplanned hospital admission due to acute decompensation, development of complications (e.g. atrial arrhythmias) and short life-span. Neurohormonal antagonists slow (but probably rarely prevent) this progression, thereby delaying death and avoiding or postponing hospital admissions [1,2]. The effect of these drugs on patients' symptoms is less well defined and that on functional capacity less convincing [3,4]. Implantable cardioverter defibrillators (ICDs) also reduce the risk of sudden death, which causes a larger proportion of deaths in patients with mild HF, compared to those with severe HF. In a subset of patients with more severe symptoms, cardiac resynchronisation therapy (CRT) has recently been shown to offer further improvements in symptoms, mortality and morbidity.

Despite the beneficial effects of neurohormonal antagonists, ICDs and CRT, many patients eventually progress to an advanced stage, characterised by severely limiting symptoms, marked haemodynamic impairment, frequent hospitalisations and high mortality. The extension of life provided by neurohormonal antagonists or the direct effect of these drugs (or a combination of both) also seems to have led to certain complications (e.g. anaemia and renal dysfunction) becoming a prominent feature in the growing number of long-term survivors with HF. This emerging cohort of patients with advanced chronic heart failure (ACHF) represents a new population for which additional treatment is required.

Despite its growing importance, not enough is known about the characteristics and optimal management of ACHF. The aims of this document are to propose a clinical definition of this condition and to describe its main characteristics.

This summary is based on a full document, which includes more background information and further references. The full report is available on the HFA, ESC website, http://www.escardio.org/bodies/associations/HFA/ and should be used when in doubt or when further information is required.

2. Definition of ACHF

2.1. Definition

ACHF may be defined as a chronic, but not necessarily irreversible, condition. Regardless of its aetiology, it is usually characterised by all the features shown in Table 1 [5–10].

A comparison with other classifications of HF is shown in Fig. 1.

2.2. Comparison with previous definitions

In 1998, Adams and Zannad first defined advanced HF as requiring a resting LV ejection fraction (LVEF) < 30% and New York Heart Association (NYHA) functional class III to IV or a peak oxygen uptake (VO_2) < 14 ml/kg/min. Additional criteria were also provided [11]. We believe that this definition should be updated. It does not incorporate subsequent advances both in diagnosis (plasma BNP and NT-ProBNP) and in treatment (beta-blocker therapy). We believe that its two main criteria (LVEF < 30%, and peak VO_2 < 14 ml/kg/min) do not justify a

Table 1
Definition of ACHF

1. Severe symptoms of HF with dyspnoea and/or fatigue at rest or with minimal exertion (NYHA functional class III or IV)
2. Episodes of fluid retention (pulmonary and/or systemic congestion, peripheral oedema) and/or of reduced cardiac output at rest (peripheral hypoperfusion)
3. Objective evidence of severe cardiac dysfunction, shown by at least one of the following:
   a) A low LVEF (<30%),
   b) A severe abnormality of cardiac function on Doppler-echocardiography with a pseudonormal or restrictive mitral inflow pattern [5];
   c) High LV filling pressures (mean PCWP > 16 mm Hg, and/or mean RAP > 12 mm Hg by pulmonary artery catheterisation) [6],
   d) High BNP or NT-ProBNP plasma levels, in the absence of non-cardiac causes.
4. Severe impairment of functional capacity shown by one of the following:
   a) Inability to exercise,
   b) 6-MWT distance < 300 m [7] or less in females and/or patients aged ≥ 75 years [8]
   c) peak VO_2 < 12 to 14 ml/kg/min [9,10]
5. History of ≥ 1 HF hospitalisation in the past 6 months
6. Presence of all the previous features despite "attempts to optimise" therapy including diuretics, inhibitors of the renin–angiotensin–aldosterone system, and beta-blockers, unless these are poorly tolerated or contraindicated, and CRT, when indicated.

Abbreviations: ACHF, advanced chronic heart failure; NYHA, New York Heart Association; LV, left ventricular; EF, ejection fraction; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; BNP, brain natriuretic peptide; NT, N-terminal; 6-MWT, 6-minute walk test; VO_2, oxygen consumption; CRT, cardiac resynchronisation therapy.

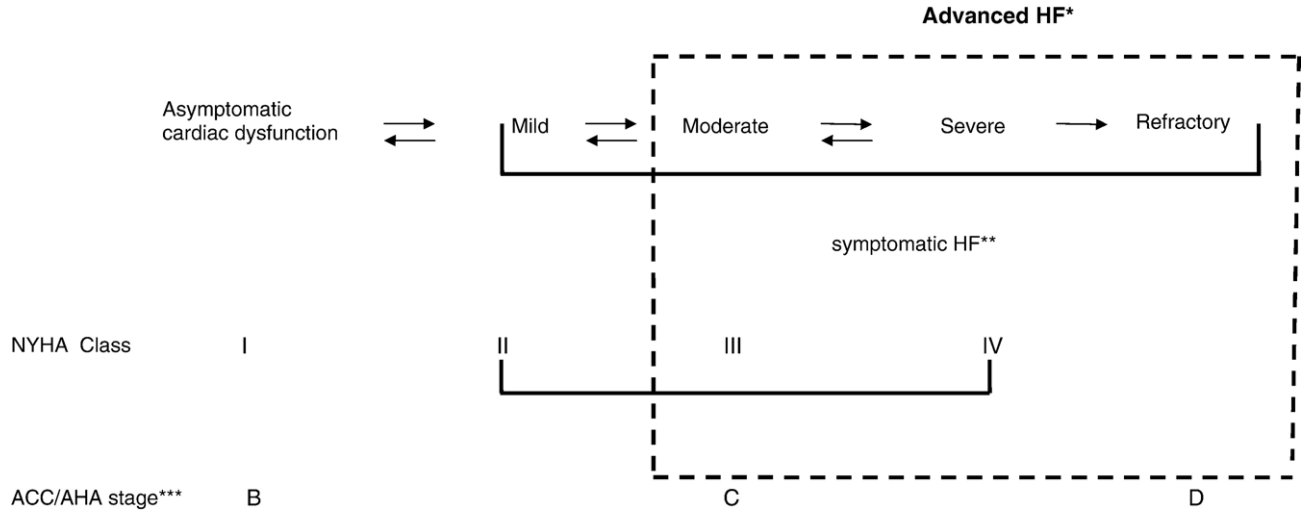

Fig. 1. Comparison between advanced heart failure and other classifications of heart failure. *See Table 1 for further components of the definition of advanced HF, including evidence of severe cardiac dysfunction, evidence of fluid retention/hypoperfusion, severely reduced functional capacity and hospitalisation for HF within 6 months, despite optimum tolerated pharmacological and device treatment. **This document concerns *chronic* heart failure. Patients may move between stages/classes in either direction but the natural history of heart failure is usually one of progressive worsening over time. ***Stage A = "at high risk of HF but without structural heart disease or symptoms of HF" [2].

diagnosis of advanced HF in the absence of a significant clinical history. Patients with a peak $VO_2 < 14$ ml/kg/min [8,10], and/or in NYHA class III to IV, with a LVEF < 25% may have an annual mortality rate of only 11–12% if euvolaemic and treated with beta-blockers and ACE inhibitors [12,13]. Indeed, patients with a normal LVEF and a recent HF hospitalisation may have a poorer prognosis [14,15].

More recently, an American expert group defined advanced HF as a "state in which patients have significant cardiac dysfunction with marked symptoms of dyspnoea, fatigue, or symptoms relating to end-organ hypoperfusion at rest or with minimal exertion despite maximal medical therapy" [16]. This definition is similar to the one that we propose, but does not include the criterion of a previous hospitalisation and does not try to objectively assess the impairment of cardiac dysfunction and functional capacity.

2.3. Comparison with other clinical presentations of heart failure

2.3.1. Acute heart failure

Acute HF is a much broader entity than ACHF although these patients may experience acute decompensation [17]. ACHF refers to a stage of the chronic syndrome whereas acute HF refers to a single episode which may be the patient's first presentation with HF (and even its only presentation, if the cause is reversible) or an episode of deterioration occurring during the chronic syndrome.

2.3.2. Refractory heart failure

Stage D refractory HF is a condition included in the ACC/AHA guidelines [2] where it is defined by the presence of marked symptoms at rest despite maximal medical therapy. Our definition of ACHF includes stage D of the US classification (Fig. 1). Both refer to an advanced stage of the disease in which the assessment of new therapies, like mechanical circulatory support, procedures to facilitate fluid removal, or new parenteral agents, may be warranted [2].

2.3.3. End-stage HF

End-stage HF indicates an extremely advanced condition where no improvement with conventional HF treatment is possible and palliative care or "ventricular assist systems" or heart transplantation (Htx) is indicated. This condition should be distinguished from ACHF in which a certain degree of reversibility may be present.

3. Clinical characteristics and diagnosis of ACHF

3.1. Symptoms and signs

Many patients with HF present for the first time with severe symptoms and signs of marked volume overload or even, acutely, pulmonary oedema. A very low left ventricular ejection fraction (LVEF) may be present. These patients usually do not have ACHF. Treatment with diuretics, neurohormonal antagonists (ACE inhibitors, beta-blockers, aldosterone antagonists and angiotensin receptor blockers) and, in certain cases, devices, will stabilise and improve the patient's condition in most cases. If initially low, LVEF will also usually increase. Thus, critical to the definition of ACHF is *persistence* of severe symptoms, functional limitation and cardiac dysfunction *despite* optimal therapy.

Only patients who remain symptomatic at rest (NYHA class IV) or on minimal exertion (NYHA class III) despite optimal drug and device therapy should be considered to have ACHF. The definition of optimal therapy may change over time as the patients' condition advances. For example

spironolactone may not be indicated in a patient presenting initially in NYHA class II but should be used, if tolerated, if the patient progresses to NYHA class III.

The development of renal dysfunction and hypotension may prevent the addition of new neurohormonal antagonists or even necessitate the withdrawal of existing drugs. Diuretic requirement may vary and careful titration is often required to avoid volume overload and also volume depletion. A combination of oral diuretic therapy and intermittent intravenous treatment (with regular monitoring) may be needed. This careful adjustment of therapy may allow symptom relief and freedom from congestion for relatively long periods of time. However, patients with ACHF are frequently hospitalised for decompensated HF. As the patient's condition advances other complications such as anaemia, generalised wasting (cardiac cachexia) and renal failure may develop.

3.2. Systolic versus diastolic left ventricular dysfunction

Severe cardiac dysfunction is prerequisite for diagnosing ACHF. Recent studies, however, have shown that up to 30%–50% of patients admitted with acute HF may have preserved LVEF [14,15,18–21]. Patients with preserved LVEF have a high rate of rehospitalisation and a similar, or only slightly lower, mortality, compared to patients with low LVEF [14,15]. Although their poor outcomes may be caused by a higher prevalence of co-morbidities, some patients with normal LVEF may progress to ACHF. However, it is important to exclude non-cardiac causes of symptoms and reversible causes of myocardial dysfunction, such as ischaemia or valvular heart disease, in these patients. Therefore, the diagnosis should also be based on the demonstration of high LV filling pressures, high plasma levels of BNP or NT-ProBNP or, more recently, on abnormalities of Doppler-echocardiographic indices of diastolic function and/or LV long-axis function (Table 1) [1].

3.3. Echocardiographic assessment

3.3.1. Systolic function

The simplest index of global LV haemodynamic pump function is LVEF. However, when used alone, it is an inadequate summary of global systolic function because, even when LVEF is normal and in the presence of small LV volumes, there may be significant LV relaxation abnormalities, longitudinal fiber dysfunction, as well as severe non-uniformities. LVEF should, ideally, be reported together with a ventricular volume — preferably end-systolic volume, indexed for body surface area as well as with echocardiographic long-axis measurements.

In some patients, LV global haemodynamic pump function may be "preserved" (usually defined as an LVEF $\geq$ 45–50%), despite reduced LV long-axis systolic shortening [22,23], because there is an accompanying increase in sphericity and in radial systolic function. Thus, full echocardiographic characterisation of LV systolic function should, ideally, include measurement of LV long-axis function.

3.3.2. Diastolic function

The simplest assessment of LV filling is obtained by recording the ratio of flow velocities across the mitral valve during early diastole and during atrial filling (*E*/*A* ratio). This ratio increases in HF as the left atrial pressure rises. When the *E*/*A* ratio is >1 because of a high left atrial pressure, the mitral inflow pattern is described as "pseudonormal". This can be distinguished from a true normal pattern if the *E*/*A* ratio reverts to <1 with LV pre-load reduction. Additional indices of diastolic function include the deceleration time (DT) of early diastolic mitral inflow. In ACHF, the most severe pattern of diastolic dysfunction is restrictive filling which is characterised by a very high mitral *E*/*A* ratio (>2) and a short mitral DT (<140 ms). This pattern reliably predicts a poor prognosis, especially if it persists after pre-load reduction [24].

Newer indices of diastolic function are useful in clinical practice because they are less load dependent. Perhaps the most useful of these is the ratio of the mitral *E* velocity to the velocity of mitral annular motion during early diastole recorded using pulsed Doppler-echocardiography (*E*/*e*′ or *E*/Ve). This index has been validated extensively and correlates well with LV filling pressure [25]. Other methods are based on the study of pulmonary venous flow. Recently, left atrial volume has emerged as a very useful simple test since dilatation reflects a chronic increase in pressure.

3.4. Natriuretic peptides and other biomarkers

BNP is released predominantly from the LV failing myocardium and correlates with HF severity. BNP or NT-proBNP may be useful to assess prognosis and to tailor therapy. This hypothesis is currently being tested in randomised trials [26,27].

Other plasma biomarkers related to inflammation or neurohormonal activation may be used to assess prognosis in patients with ACHF. Cardiac troponins are released by a significant percentage of patients with HF of either ischaemic or non-ischaemic aetiology, and may be important for prognosis.

3.5. Exercise testing

By definition, patients with ACHF are in NYHA class III or IV, implying severe functional limitation. The extent of functional limitation can be further defined by formal exercise testing.

3.5.1. Cardiopulmonary exercise (CPX) testing

Peak VO_2, frequently adjusted for gender, age, and body weight, and ventilatory response to exercise, usually measured as the slope of regression line relating minute ventilation (VE) to carbon dioxide production (VCO_2) (VE–VCO_2 slope) [28–30] are the CPX derived parameters most often used in clinical practice.

CPX is commonly used to stratify the risk of death in patients with HF and to identify candidates for Htx. Low peak VO_2 implies a poor outcome, independently of other risk factors [8,10,28,31,32]. Nevertheless, its optimal cut-off point for risk stratification is still debated [28,31,32]. It is generally agreed that peak $VO_2 > 18$ ml/kg/min identifies low risk patients, whereas values ≤ 10 ml/kg/min indicate those with severe functional impairment, poor outcome and a potential indication for Htx [10,28,31]. A cut-off value of 14 ml/kg/min has also been used to identify those with a potential indication for Htx [8,10,28,33], although this threshold may no longer be valid because it was derived from older studies in which patients were not treated with beta-blockers, ICDs or CRT. A lower value of 12 ml/kg/min has been suggested for the indication to HTx in patients on beta-blocker treatment [10]. We also suggest using this lower value as a criterion for ACHF in patients on beta-blocker treatment (Table 1). Additional CPX derived indices (i.e. VE–VCO_2 slope) may identify patients at high risk of subsequent events. A combination of peak VO_2 with other clinical prognostic markers is also useful [1,10,28,31].

3.5.2. Six-minute walk test

The 6-minute walk test (6-MWT) distance is another measure of functional capacity which correlates with quality of life and with more objective measures derived from maximal CPX [7,28,34]. A 6-MWT distance < 300 m implies severe impairment, associated with a poor outcome, whereas a distance > 500 m indicates moderately preserved exercise capacity and a low risk of events [7,34]. However, age, gender, and body mass index have an important influence on 6-MWT performance [8,35] and this must be considered when this test is used for the assessment of HF patients.

A significant number of patients with ACHF may not be able to provide a 6-MWT or may have a contraindication to exercise testing. This group has uniformly bad prognosis [28,31].

The value of the 6-MWT and CPX as methods of evaluating treatment in ACHF has not been assessed.

3.6. Hospitalisations

Hospitalisation rates, including number and duration of admissions, are a very simple and important prognostic index in patients with HF. Hospitalisation, especially due to worsening HF, implies an unstable clinical course and a high short-term probability of major events including death [19–21,36,37].

3.7. Assessment of prognosis

The prognosis of patients with severe HF has improved substantially in recent years but it remains poor. Useful prognostic indicators are outlined in Table 2 [1,2,7,8,10,19–21,24,28,31,32,37–40]. Signs of increased LV filling pressure and/or of right ventricular dysfunction, assessed by Doppler-echocardiography or cardiac catheterisation, are more important in ACHF with a greater predictive power when these data are collected after optimisation of therapy [6,24,41]. Risk-stratification models have been developed and validated both in patients referred for Htx and in those hospitalised for HF. Co-morbidities, blood pressure and renal function are often amongst the most important independent prognostic variables [20,21,38–40,42]. These results can also be applied to patients with ACHF.

Table 2
Prognostic determinants in patients with ACHF

Demographic
▪ Advanced age
▪ Male gender
Clinical
▪ Frequent rehospitalisations
▪ Advanced NYHA class
▪ Intolerance to neurohormonal antagonists
▪ Persistent/relapsing signs of pulmonary or peripheral congestion
▪ Hypotension
▪ Co-morbidities (diabetes, renal failure, hepatic failure, anaemia, COPD, etc.)
Electrocardiography
▪ Resting tachycardia
▪ Wide QRS complex
Laboratory
▪ Hyponatraemia
▪ Renal insufficiency (BUN/serum creatinine)
▪ Anaemia
▪ Hepatic insufficiency
▪ Neurohormones (norepinephrine, endothelin...)
▪ Natriuretic peptides
▪ Cardiac myocyte necrosis markers (troponins)
▪ Inflammatory markers (CRP...)
Doppler-echocardiography and right heart catheterisation
▪ Low LV EF/increased LV ESVI
▪ Decreased LV long-axis systolic shortening
▪ Mitral regurgitation/increased left atrial volume
▪ Signs of increased LV filling pressure
▪ Low RV EF
▪ Increased pulmonary vascular resistance
Functional capacity
▪ Inability to perform an exercise test
▪ Low peak VO_2 (ml/kg/min, percentage of predicted age, gender, body weight adjusted values)
▪ Increased ventilatory response to exercise (VE/VCO_2 slope)
▪ Low 6-minute walk test distance

Abbreviations: COPD, chronic obstructive pulmonary disease; LV, left ventricular; EF, ejection fraction; ESVI, end-systolic volume index; RV, right ventricular.

4. Treatment of ACHF

4.1. Medical treatment

One key component of our definition of ACHF is that patients are receiving guideline-recommended and individually optimised medical treatment. There is evidence that neurohormonal antagonists are administered at lower rates and at lower doses in patients with more severe HF [43] and this may have a detrimental effect on prognosis [44]. It is

therefore important to make every attempt to initiate and up-titrate all indicated medications to the doses shown to be effective.

4.1.1. ACE inhibitors

Patients with ACHF may be more likely to develop symptomatic hypotension and/or renal insufficiency and such intolerance to ACE inhibitors is an ominous prognostic sign [45]. The benefits of these agents are so important that every effort should be made to use them. Modest increases in serum creatinine (e.g. an increase of ≤50% from baseline or to ≤266 μmol/l [3 mg/dl], which ever is the smaller) or asymptomatic hypotension are not contraindications to continued treatment. Recommendations to minimize side effects are given in guidelines [1,2] and practical guidance documents [46].

4.1.2. Beta-blockers

The benefits of beta-blockers are at least as great in patients with severe HF as in those with less advanced disease [12,13].

The initiation of beta-blockers is contraindicated in patients with acutely decompensated HF [1,2,17]. In patients who develop acutely decompensated HF while on chronic beta-blocker therapy, the dose of these agents may be reduced, or they may be temporarily withdrawn, but treatment should be re-started as soon as clinical conditions stabilise. Starting (or re-starting) beta-blocker treatment during the HF hospitalisation is associated with a shorter titration phase and better compliance [47].

In patients developing intolerance, thought to be due to depressed LV systolic function, during initiation beta-blockers, some authors advocate the use of concomitant inotropic support although this is an unproven approach. Phosphodiesterase inhibitors (PDE-I) and levosimendan are the drugs of choice as their action, unlike dobutamine, is independent from the beta-receptors [17,48].

4.1.3. Angiotensin receptor blockers (ARBs)

ARBs are a good alternative to ACE inhibitors in symptomatic patients who do not tolerate them [1,2]. Based on data from randomised trials [49,50], ARBs are also indicated in addition to beta-blockers and ACE inhibitors in patients who remain symptomatic, although careful monitoring of potassium and renal function is mandatory [1,2,46].

4.1.4. Aldosterone antagonists

Aldosterone antagonists are indicated in patients with NYHA class III to IV HF caused by LV systolic dysfunction [1,2,51]. They should be avoided in patients with severe renal failure (serum creatinine>221 μmol/l [2.5 mg/dl]) and/or hyperkalaemia (serum potassium>5.0 mmol/l). Careful monitoring of renal function and serum potassium levels is mandatory. The effects of aldosterone antagonists on blood pressure are smaller than ARBs.

4.1.5. Triple and quadruple combinations of neurohormonal antagonists

The combination of three neurohormonal antagonists should be attempted in all patients with ACHF. All patients should receive an ACE inhibitor and beta-blocker unless there is intolerance. Either an ARB or an aldosterone antagonist should then be added. There is no evidence regarding which are the preferred agents to use in combination. Both spironolactone and candesartan have demonstrated benefits on mortality when added to an ACE inhibitor [50,51].

The use of four neurohormonal antagonists (i.e. ACE inhibitor, beta-blocker, ARB and aldosterone antagonist) is not evidence-based and the safety and efficacy of these agents used together are uncertain. If used, careful monitoring of blood pressure, renal function and serum potassium is mandatory.

4.1.6. Diuretics

High doses of loop diuretics are often necessary in the patients with ACHF. When used intravenously, continuous infusion of loop diuretics is more efficient than bolus therapy [17]. The combination of a thiazide or spironolactone with loop diuretics has been proposed to overcome diuretic resistance [17]. Metolazone has been advocated as an alternative to thiazide diuretics as it remains effective at low glomerular filtration rates [17].

Since high doses of diuretics are associated with adverse effects, including dehydration, renal dysfunction, hypokalaemia and gout, the need for continued high dose treatment should be reconsidered once signs of congestion have resolved. Patients should then be maintained at the lowest dose that can keep them clinically stable and free of congestion (at their "dry weight") [1,2,17,46]. Careful monitoring of renal function and serum electrolytes is mandatory in any patient, but particularly important when high doses or combinations of diuretics are used.

Ultrafiltration has been shown to be a safe and effective treatment to reduce congestion in patients with decompensated HF and diuretic resistance [52].

4.1.7. Nitrates

In ACHF, oral nitrates can be used to relieve concomitant angina but only have a long-term benefit on survival and hospitalisation when used in conjunction with hydralazine [53]. In the African-American Heart Failure Trial, a fixed dose combination of isosorbide dinitrate and hydralazine reduced all-cause mortality and HF hospitalisations and improved quality of life, compared to placebo, in 1050 black patients with NYHA class III or IV HF on optimal medical treatment including diuretics and neurohormonal antagonists [54].

4.1.8. Digoxin

Digoxin is indicated in patients with HF and concomitant atrial fibrillation. In the Digitalis Investigation Group (DIG) trial, digoxin reduced HF hospitalisations but not mortality

in HF patients in sinus rhythm treated with diuretics and ACE inhibitors. As frequent hospitalisations are among the hallmarks of ACHF, digoxin is indicated in most patients with ACHF. Further analyses have indicated different effects of digoxin on mortality, with a reduction versus placebo at low serum digoxin levels, and no effect at higher plasma levels [55]. However, since renal impairment is frequent in ACHF, daily dosage should be adapted accordingly.

4.1.9. Other inotropic agents

Temporary inotropic support using intravenous sympathomimetic agents, PDE-I or levosimendan, can be considered in patients who have evidence of severely reduced peripheral perfusion with or without pulmonary congestion [1,2,17]. Despite short-term haemodynamic improvement, these agents may have an adverse effect on mortality [56] and cause supraventricular and ventricular tachyarrhythmias [57]. Thus, they should be administered only when indicated (signs of peripheral hypoperfusion), at the lowest effective doses and for the shortest duration of time as possible [17].

4.1.10. Anti-platelet and anti-thrombotic agents

Atrial fibrillation is more common in patients with more severe HF and, in the absence of a contraindication, warfarin should be given to reduce the risk of thromboembolism [58]. The use of warfarin in other patients is not evidence-based although most clinicians will also use warfarin in patients shown to have left ventricular thrombus on an imaging study.

Aspirin should be considered in patients with coronary artery disease or with atrial fibrillation and contraindications to oral anticoagulation [58]. Some authors take the view that there is no robust evidence supporting long-term use of aspirin in patients with HF and suggest that it may even have detrimental effects, possibly by antagonising the effect of vasodilator prostaglandins and the actions of ACE inhibitors. Although this view is controversial, there is evidence that patients treated with aspirin may have an increased risk of hospital admission due to worsening HF [59,60].

4.1.11. Cardiac resynchronisation therapy (CRT)

The indications to implantable cardioverter defibrillators and CRT have been thoroughly discussed in guidelines [1,2]. CRT, with [61] or without [62] combined ICD, has been shown to reduce mortality and hospitalisations and improve symptoms and quality of life in patients with NYHA class III to IV HF, reduced LVEF and wide QRS duration. It should therefore be considered in ACHF patients with these characteristics. The importance of mechanical dyssynchrony, independently from QRS duration, remains to be investigated.

4.1.12. Implantable cardioverter defibrillator (ICD)

As HF progresses the risk of death from pump failure, relative to sudden, presumed arrhythmic, death increases. There is also evidence that the benefit of an ICD is less in patients with advanced HF. In the SCD-HeFT trial there was statistically significant heterogeneity in the effect of ICD therapy according to baseline NYHA class, with no reduction in mortality in patients in functional class III [63]. It is however possible that this result was related to the lower number of patients in NYHA class III. Though underpowered, the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial showed opposite results, with the largest reduction in mortality in NYHA class III patients [64].

Probably the most important factor determining the indication for ICD implantation in a patient with advanced HF is her/his life expectancy. Analyses of controlled trials have shown the time dependency of the beneficial effects of ICDs on mortality, with a lack of benefit in the first months after implantation and an exponential rise in benefit thereafter reaching a peak after 3 years [65]. Accordingly, economic analyses have shown that it may need up to 6–7 years of follow-up to be cost effective [66,67]. Thus, ICDs may not be indicated in patients with ACHF and a predicted short life expectancy. This approach is, however, not considered in current guidelines and not evidence based.

In a patient with an ICD who progresses to terminal heart failure, the physician, patient and family/carers may decide to inactivate the device.

4.1.13. New agents

The potential role and the risk/benefit ratio of some newer agents have not yet been established. The vasodilator nesiritide, a recombinant human B-type natriuretic peptide, improved haemodynamics and symptoms in patients with acute HF but its long-term effects have not been assessed sufficiently. It is approved for treatment of acutely decompensated HF in US but not in Europe [17]. Other natriuretic peptides, like urodilatin, are currently under investigation [68].

Tolvaptan is a selective antagonist of vasopressin V2 receptors. It increases water permeability of the renal collecting tubules, thereby promoting excretion of retained water and weight loss and normalizing hypoosmolar hyponatraemia. Its efficacy on symptoms and clinical course is currently under investigation [69].

Adenosine A1 receptor antagonists may increase diuresis and improve renal function in patients with ACHF [70].

Drugs that block lipid oxidation may produce a preferential shift to intracellular glucose utilization, which is energetically more efficient. Some of these drugs, perhexilene [71] and trimetazidine [72], might have favourable effects in patients with severe HF.

Statins have many potentially beneficial effects in patients with ACHF. Their effects on outcomes are currently being tested in large multicenter trials [73,74].

4.2. Treatments that should be discontinued

Discontinuation of unnecessary hypotensive agents such as nitrates, calcium channel blockers and alpha adrenoceptor antagonists, can facilitate introduction and/or up-titration of neurohormonal antagonists. A number of medicines have either demonstrated adverse effects in patients with HF or there

are theoretical reasons for caution. These effects are mediated by a variety of mechanisms, including fluid retention, reduced contractility, potential pro-arrhythmic effects, direct cardiotoxicity and drug–drug interactions [1,2,75].

4.3. Disease management programmes

Disease management programmes improve the care and outcomes of patients with ACHF. Their key components are a multidisciplinary approach including adequate education for patients and carers, frequent monitoring of clinical status, and careful assessment of patient's compliance to therapy. Disease management programmes have been consistently shown to be associated with a reduction in hospitalisations and, in some studies and meta-analyses, mortality [1,2,16,76]. The ESC guidelines give HF management programmes a strong recommendation [1].

4.4. Surgical strategies

4.4.1. Heart transplantation (Htx)

Htx is indicated in patients with severe symptoms of HF for whom no additional medical or surgical treatment is possible, including CRT, and in whom life expectancy is less than one year. Contraindications to heart transplantation have been summarised in recent guidelines [1,2,10].

4.4.2. Mechanical support

Mechanical circulatory assist devices were developed to sustain the circulation in patients awaiting Htx (*bridge to transplant*) [77]. Implantable LV assist devices (LVADs) allow many patients to survive until the time of transplantation, and pre-operative recovery of haemodynamic and nutritional status improves post-operative survival. Occasionally, LVADs may improve myocardial function so effectively that the device can be removed and transplantation is no longer required (*bridge to recovery*). In selected patients with end-stage HF due to idiopathic dilated cardiomyopathy, weaning from a LVAD is a clinical option with good long-term results. The ultimate goal of the implantable LVAD is to provide an alternative to cardiac transplantation (*destination therapy*) [78].

4.4.3. Other surgical interventions

Revascularization is presently only indicated for symptomatic myocardial ischaemia and can be performed successfully in patients whose LVEF is $\leq 30\%$, with a low hospital mortality [79]. Until the results of ongoing randomised trials are reported [80], revascularization is not indicated for other putative reasons such as "hibernating myocardium". Treatment of secondary mitral regurgitation by undersized mitral annuloplasty is another intervention being tested in a randomised trial. This is also the case for surgical LV restoration, which reduces LV volume and restores its elliptical shape, and can be accompanied by revascularization. Myocardial restraint devices are also currently under investigation [81].

Table 3
Priorities for clinical research in ACHF

A. Epidemiology
- Incidence and prevalence
- Prognosis
- Prognostic variables

B. Role of LV systolic dysfunction
- Clinical presentation, pathophysiology, and outcome of advanced HF in patients with either poor LV systolic function or a normal EF

C. Role of plasma biomarkers
- Utility of measuring natriuretic peptides for diagnosis and prognosis
- Utility of measuring other neurohormones or biomarkers
- Comparison with clinical assessment

D. Prognosis
- Search for new prognostic indicators
- Comparison of the relative prognostic value of clinical, laboratory, echocardiographic and exercise capacity indices
- Comparison of the value of repeated measurements of these indices for prognosis and optimising medical treatment

E. Treatment
- Randomised controlled trials of novel pharmacologic and device interventions

F. End-of-life care
- Patients preferences for end-of life care and experiences of having advanced heart failure (symptom perceptions, quality of life, thoughts about death and dying)
- Controlled trials evaluating the effects of combining palliative care and specialist follow-up in advanced and end-stage heart failure

4.5. End of life

The goal of end-of-life care is to control debilitating symptoms and manage distress. In The Regional Study of Care for the Dying, the most commonly reported symptoms in the months prior to death were pain, dyspnoea, low mood, sleeplessness, and anxiety [82]. Agents which may help palliate symptoms, include opiates, inotropes and diuretics.

Although health care systems and laws differ from country to country, issues surrounding end-of-life care for patients with HF are similar and deserve attention. The anticipated course of the disease (including prognosis), treatment options (including resuscitation and ICD inactivation) and planning of treatment and care (including hospice care, if available) should be discussed with the patient and family before he/she becomes too ill to participate in decision-making. Advance directives are decisions about desired treatments made by individuals and shared with loved ones and health care providers, although any decisions made should be reassessed at regular intervals as they may change over time [16,83].

5. Priorities for clinical research

This position statement identifies many questions, that are as yet unanswered. Much remains unknown about the epidemiology, diagnosis, prognosis, and treatment of patients with ACHF. Particular areas that may merit further investigation are shown in Table 3.

Acknowledgement

We wish to thank Inge Torfs for her assistance in the preparation of the manuscript.

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