End stage chronic heart failure

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Summary

Congestive heart failure (CHF) has kept its progressive nature despite significant advances in therapy. With more advanced disease, medical therapy is broadened. Even so, some patients remain severely symptomatic. However, before additional action is taken, it should be regarded if therapy really fails. Often, therapy is not increased sufficiently because of assumed rather than actual intolerability. Thus, increase in serum creatinine up to 30–50%, hyperkaliemia up to 5.5 mmol/l, and asymptomatic hypotension and bradycardia are usually acceptable. Cautious and slow start and uptitration are the more important the more severe heart failure is, but these patients also profit most from this therapy. If patients remain severely symptomatic despite adequate medical therapy, cardiac resynchronisation therapy (CRT) should be considered. It significantly improves both symptoms and prognosis. Although implantable defibrillators (ICD) are less effective in end-stage CHF, CRT and ICD may be combined as CRT may improve function status, making patients eligible also for ICD therapy. In selected patients, heart transplantation is still an option if no other therapeutic options are effective and there are no contraindications. In these patients, prognostic assessment of CHF is particularly important. Assist devices are used as bridge to transplant or more seldom to recovery only in many countries, but destination therapy may become more important in future therapy with improved devices. Many other therapies are under investigation at present. Thus, therapeutic options for end-stage CHF may further broaden in the near future.

Key words: heart failure; end-stage disease; device therapy; prognosis; heart transplantation

Introduction

Congestive heart failure is the final common pathway of most heart diseases. It is very common, ie up to 2% of the total population are affected. Despite significant advances in the therapy in the last 2 decades as delineated in the recent guidelines by the European Society of Cardiology [1], heart failure has kept its progressive nature and morbidity and mortality remain high. In fact, prognosis is worse than for most cancers, and end stage heart failure is comparable with the most malignant neoplasms.

Stages of heart failure have been classified

Figure 1

Stages in the development of heart failure from risk factors of heart failure to end stage disease, underscoring the progressive nature of the disease and the consequences in therapy. CAD: Coronary artery disease, MI: Myocardial infarction, LVH: Left ventricular hypertrophy, LVEF: Left ventricular ejection fraction, ACE-I: Angiotensin converting enzyme inhibitors, BB: Beta blockers, LVAD: Left ventricular assist device (adapted from [2]).
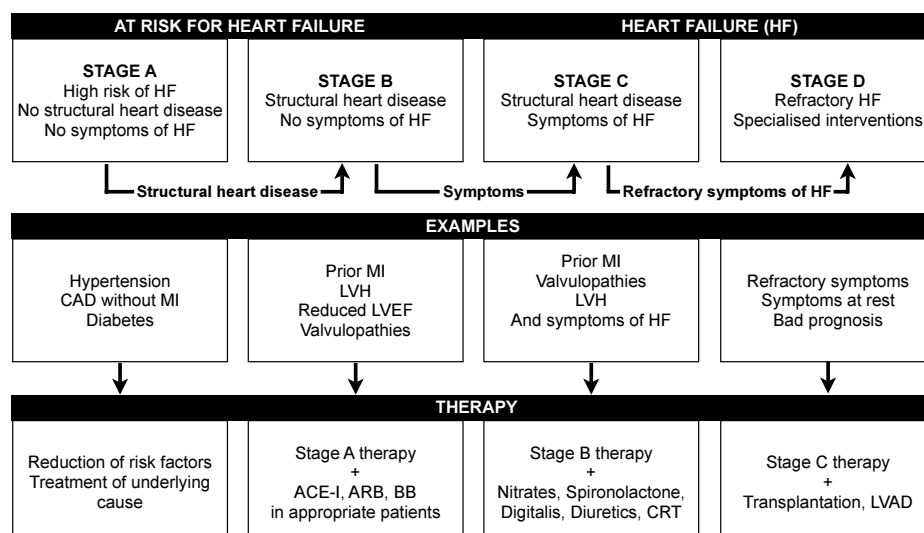
from presence of risk factors prior to development of heart failure to end stage disease (figure 1 [2]). Medical treatment has been widely studied in many large trials primarily in stages B and C. More recently treatment of end stage heart failure (stage D) was investigated, which often proved difficult. The present article summarises most recent advances in chronic end stage heart failure.

What to do if standard therapy fails?

Patients who no longer respond to medical treatment with ACE-inhibition (or alternatively angiotensin-II antagonism) and β-blockade or who remain significantly symptomatic (NYHA III) require additional therapy with spironolactone (or eplerenone if not tolerated) [3]. Another treatment option in symptomatic patients is adding an angiotensin-II receptor blocker [1]. CHARM-Added showed a significant reduction in the primary outcomes, as well as the total number of hospital admissions for CHF after the addition of an angiotensin-II receptor antagonist to an ACE-inhibitor and other treatment including baseline β-blockade [4]. However, the combination of all three available agents inhibiting the renin-angiotensin-aldosterone system, ie ACE-inhibitor, angiotensin-II receptor blocker, and spironolac-

tone, may carry a significant risk of hyperkaliaemia and renal failure and should, therefore, only be used in selected patients under close monitoring [5]. Moreover, the effect of adding spironolactone and angiotensin-II receptor blocker has not yet been investigated. Since the benefit of spironolactone was larger [3] than the one found in CHARM-Added [4], spironolactone is often preferred in patients NYHA class ≥III.

For symptomatic reasons, diuretics, digoxin, and nitrates may be used. Despite these interventions, some patients remain significantly symptomatic, show progression of disease, or develop repeated decompensations. These patients have poor prognosis as well as quality of life, and, as a consequence, need further assessment and treatment.

Does it really fail?

Patients remaining symptomatic under above mentioned treatment are often found not to receive full doses as investigated in large clinical trials and recommended by guidelines [1]. Assumed intolerability for particular drugs or higher doses is usually the reason for not giving recommended therapy. However, assumed intolerability does not always correspond to actual intolerability. Thus, most patients referred for transplant evaluation to a single centre were on recommended drugs. In particular, recently published studies had a direct influence on prescription of these drugs, but doses given were not appropriate and did not change over time. Interestingly, further increase in dose was possible in most patients despite assumed intolerability [6].

Misconception is the most likely reason for this behaviour of treating physicians. The lack of increase in standard medical treatment is not always rational and not corresponding to clinical findings [5]. Thus, an increase of serum creatinine after starting an ACE-inhibitor or angiotensin-II receptor blocker is often interpreted as renal damage. In fact, the slight functional deterioration is related to the mode of action of these drugs and represents preservation of long-term renal function [7] and reduction in microalbuminuria [8]. Indeed, patients with renal failure profit from inhibition of the renin-angiotensin system in that renal

function is preserved. Even in advanced renal failure, ACE-inhibition is beneficial [9]. Thus, an initial increase of the serum creatinine of up to 30% or even slightly more is tolerable. However, the dose of renally excreted ACE-inhibitors has to be adapted to renal function. Also, hyperkalaemia, as often seen particularly in combination with spironolactone (or eplerenone), is acceptable up to 5.5 mmol/l. Close monitoring of both serum potassium and creatinine remains eminent, especially 4 to 7 days after each change in therapy.

ACE-inhibitors are also often accused to cause dry cough. Indeed, ACE-inhibitor induced cough has been reported to occur in 5 to 35% among these patients, regardless of the temporal relation between the initiation of ACE-inhibition and the onset of cough [10]. However, dry cough may be a clinical sign of worsening heart failure. Pulmonary congestion may result in obstruction and oedema of bronchi leading to dry cough. In these patients, intensification of heart failure therapy including increasing doses of ACE-inhibitor may even reduce cough [11].

Asymptomatic bradycardia is a common cause for suboptimal β-blocker doses in patients with chronic heart failure. However, asymptomatic bradycardia and AV-block grade I are no reason for dose reduction or even withdrawal of therapy. Experimental studies have shown that bradycardia

is a major mechanism by which β-blockers restore contractile function [12]. A reduction in heart rate is a predictor of beneficial effects of β-blocker therapy independent of pretreatment heart rate [13].

Another commonly suggested reason for intolerability is hypotension. Often, there is a direct inverse relationship between severity of heart failure and blood pressure. Thus, patients with low blood pressure have most advanced disease with poor prognosis [14]. These patients profit equally from β-blockade with carvedilol regarding improvement of prognosis, but even more so symptomatically. Interestingly, treatment with carvedilol resulted in a paradoxical increase in blood pressure if initial blood pressure was ≤95 mm Hg, but not in the other patients. Therefore, hypotension per se is no reason for not initiating and up-titrating β-blockade. In these patients with advanced heart failure, however, it must be used with caution, using a low initial dose and small dose increases with sufficiently long intervals, but still aiming at target dose. Thus, the slogan "start low, go slow, aim high" is particularly true for these patients.

Chronic obstructive pulmonary disease and asthma are other major reasons for not prescribing β-blockers. The main concern is that β-blockers may precipitate severe and potentially fatal bronchospasm. However, there is general agreement that fixed or only mildly reversible bronchial obstruction is no contraindication for β-blocker use [1], since β-blockade is of no harm in these patients. In fact, a recent meta-analysis showed that cardioselective β-blockers are not only safe, but also beneficial in heart failure patients with co-existing airway disease [15]. Since in clinical practice it may be difficult to differentiate between no/mild and significant reversible broncho-obstruction, careful use and testing are advised.

Still, sometimes intensification of medical treatment is difficult, particularly in patients with end stage heart failure, advanced age and co-morbidities. Therefore, therapy should be adapted to the individual need. An interdisciplinary approach is more useful, the more complex the circumstances are. Numerous studies have shown that multidisciplinary interventions for heart failure may reduce both hospital admission and all-cause mortality [16, 17].

Nevertheless, progression of heart failure cannot be prevented in some patients with medical therapy only. These patients may profit from further treatment modalities.

Device-therapy (CRT, ICD)

Cardiac resynchronisation therapy (CRT)

Dyssynchrony of the contraction of the left ventricle is common in patients with advanced heart failure, usually caused by left bundle branch block or comparable conduction delay. In these patients, cardiac function may be improved by cardiac resynchronisation therapy (CRT) with an implantable biventricular pacemaker. This device stimulates both the right and left ventricle. The left ventricle is stimulated not only from the septum, but also from the lateral wall via an additional electrode placed through the coronary sinus, thereby harmonising the contraction. Recently, the effects of CRT on morbidity and mortality were investigated in patients with reduced left ventricular function, wide QRS-complex and/or echocardiographic signs of ventricular dyssynchrony and symptoms during daily life activities despite optimal medical therapy [18]. It revealed a dramatic reduction not only of the combined endpoint of mortality and cardiovascular hospitalisation by 37%, but also a significant survival benefit of 36%. Additionally, it was associated with a significant increase in ejection fraction, quality of life, and a reduction of symptoms. The observed benefits persist or even increase with longer follow-up [19]. Interestingly, not only death from worsening heart failure is significantly reduced, but also sudden cardiac death.

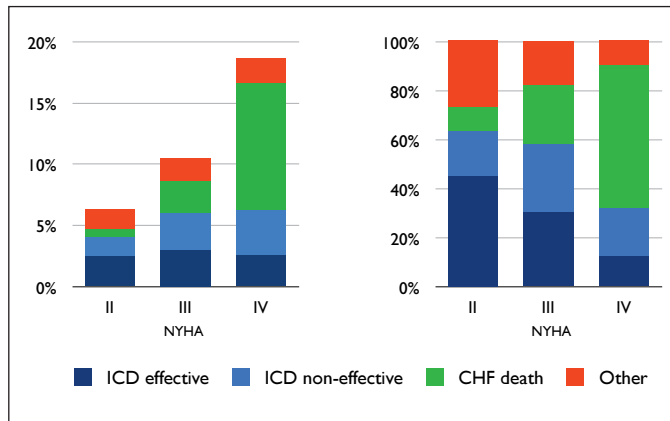Apart from very seldom complications, the main problem is that approximately 25 to 30% of the patients do not respond to CRT. The reasons for failing are not conclusively investigated yet. Lack of dyssynchroneous contraction despite wide QRS-complex might be one of the reasons. Therefore, echocardiographic evaluation is used for indication of CRT in some centres although data are not conclusive yet. Another possibility of insufficient response is the presence of extensive scar tissue in the region of left-lateral wall stimulation [20], but this needs to be confirmed. Further studies are required to prospectively address this important aspect of CRT therapy failure. Ongoing studies are also addressing the use of CRT in patients who do not meet the standard criteria.

Implantable cardioverter defibrillator (ICD)

Implantable cardioverter defibrillators are the other important component of device therapy in heart failure to prevent sudden cardiac death, although they are not used as end stage therapy. In fact, ICDs are more effective in less advanced heart failure, because sudden cardiac death is the main cause of death in less severe heart failure, whereas progression of disease is the main cause of death in end stage heart failure [21]. In addition, patients within functional class NYHA II have a much better outcome after an adequate ICD shock event than patients within NYHA class III and IV, who may die from electromechanical dissociation after-

wards ([22], figure 2). A very recent large trial underscored this theoretical consideration, as ICD-implantation was particularly effective in NYHA II patients, but not in more advanced heart failure [23].

Several large clinical trials validated the efficacy of ICD therapy in patients with reduced left-ventricular ejection fraction (≤30%), independently of the underlying cause [23, 24]. A relative reduction of on average approximately 1/3 was found. The data from these trials increased the impact on ICD treatment practices. However, initiation of medical therapy can dramatically improve ejection fraction. Thus, medical therapy should be optimised prior to implantation, which was also applied in most patients of the large ICD-trials.

Survival curves do not divert immediately after implantation, indicating that ICD should be used primarily in patients with persistently low ejection fraction under medical treatment. Electrophysiological testing is hardly necessary with the exception of some high risk patients with coronary artery disease (eg EF 30–40% and non-sustained VT) [25]. It is of utmost importance to assess left-ventricular ejection fraction several months after initiation of therapy. In patients after myocardial infarction, this time interval may be shorter than in the other heart failure patients due to the higher absolute risk in ischaemic cardiomyopathy. However, ICD-implantation was not effective immediately after myocardial infarction (ie first 40 days) [26]. In end stage heart failure, the potential relative benefit of ICD is significantly smaller (figure 2) and, therefore, may be reserved for selected patients (eg transplant candidates).

Combination of CRT and ICD

Although ICD is not most efficient in end stage heart failure, CRT may improve functional status significantly, making patients eligible also for ICD therapy. The combination of CRT with an ICD reduced the risk of all-cause mortality by 36% when compared with optimal medical therapy alone during short-term follow-up in severely symptomatic (ie NYHA ≥III) heart failure patients [27]. The combined therapy was not superior to CRT alone regarding the primary combined endpoint. However, the combined therapy significantly reduced mortality compared to patients without device. Therefore, the decision as to whether CRT is implanted alone or in combination with ICD should be tailored to the individual need of each patient.

Is heart transplantation still an option?

Despite significant improvement in heart failure therapy including extended medical and device-based therapy, some patients show progressive deterioration. In some of these patients, heart transplantation is a good therapeutic option. Importantly, patients should not be evaluated for heart transplantation before all other therapeutic options have been considered and failed [28]. This includes revascularisation in patients with coronary artery disease and significant areas of ischaemia or hibernation, although this approach has not yet been prospectively tested, or valve surgery in case of haemodynamically relevant valvulopathies.

In the last 2 decades, improvements in patient selection, surgical techniques, organ preservation, and postoperative management have increased survival rates and reduced complications after heart transplantation. Current survival rates are 83% at 1 and 72% at 5 years, with 50% of patients surviving 9.8 years [29]. However, significant problems remain, limiting the potential of heart transplantation. Thus, perioperative graft failure, particularly in patients with elevated pulmonary

Table 1

Relative and absolute contraindications for heart transplantation.

Relative factors	Absolute factors
Unusual weight loss	Fixed pulmonary hypertension
Drug, tobacco, or alcohol abuse	Active systemic infection
Advanced age (over 65–70 years)	Severe cerebral or carotid vascular disease not amenable to surgery
Severe cachexia	Severe chronic obstructive pulmonary disease or severe chronic bronchitis
Psychiatric illness which may interfere with compliance	Irreversible and severe hepatic or renal dysfunction
Morbid obesity	Unmanageable and/or severe psychiatric disease
Advanced, generalised atherosclerosis; severe peripheral vascular disease	The patient is unable to understand the issues related to transplantation and unable or unwilling to take medications as instructed
Diabetes mellitus in poor control	Active peptic ulcer disease
History of cancer (detailed information needed for evaluation)	Positive HIV test
	Active malignancy

hypertension, acute rejections though less common with current immunosuppression, infections related to immunosuppressive therapy mainly during the first year, as well as graft vasculopathy and malignancies late after transplantation are the most frequent causes of death. On the other hand, donors are limited. Therefore, careful selection of potential recipients is required.

There are important contraindications for heart transplantation (table 1) [1]. Co-morbidities significantly influence patient selection, since they may worsen prognosis or increase the risk of complications. Irreversible increase in pulmonary vascular resistance increases the risk of acute graft failure significantly. Finally, mal-compliance or substance abuse may be prohibitive for transplantation in some patients, since accurate intake of immunosuppressive therapy is vital.

Assessment of prognosis

Considering the relatively high mortality during the first year after transplantation with relative good prognosis afterwards on the one hand, and the progressive nature of end stage heart failure on the other hand (figure 3, [30]), assessment of individual prognosis is important particularly in patients referred for cardiac transplantation, but also for other therapeutic options. Importantly, evaluation for heart transplantation should not be postponed too long in end stage heart failure patients under maximised treatment, since there is a "point of no return" when transplantation is no longer possible (eg in multi-organ failure). Unfortunately,

this "point of no return" is difficult to predict, underlining the importance of prognostic assessment.

There are numerous parameters that were demonstrated to predict prognosis in heart failure. However, no single prognostic factor was found to be sufficiently predictive. In addition, results from countless trials have varied widely, because they not only depend on the population investigated, parameters assessed, and statistical method used (in multivariate analysis small differences may have a big impact), but also on changes over time and response to therapy. Therefore, assessment of an individual patient's prognosis remains difficult and should not be based on one single parameter. Also, ongoing re-evaluation process is inescapable.

Despite these caveats, various tests have been established for prognostic assessment of heart failure patients in addition to symptoms and clinical parameters such as blood pressure, heart rate, or aetiology of heart failure [31]. In particular, assessment of peak oxygen consumption (VO_2max) using ergospirometry is well established in numerous studies and generally accepted as a mainstay for assessment of potential transplant candidates. Accordingly, it is incorporated in the probably most widely used prognostic score [31]. However, this score has been developed and validated before the widespread use of CRT, ICD, β-blockers, and spironolactone. A number of studies have evaluated its prognostic value in the present era, showing that the score continues to stratify risk; however, as survival has improved with the use of these agents, the risk associated with each level has decreased [32]. Particularly in the medium risk range, further parameters may help to improve stratify risk. Ergospirometry has the additional advantage of providing further prognostic factors independent of VO_2max [33, 34]. More recently, plasma levels of B-type natriuretic peptide (BNP) have been widely investigated for prognostic assessment in patients with both chronic and acute heart failure, showing promising results [35, 36]. Although BNP-level was found to be the single most predictive parameter in most studies, it is not yet considered as generally accepted prognostic marker for transplant listing [32].

Figure 3

Comparison of patients who were taken on a waiting list for transplantation immediately after referral (Transplantation) and who were initially considered too well (Medical therapy). Although therapy of heart failure has changes since publication, these results nicely show the progressive nature of heart failure and the need for ongoing reassessment of prognosis in these patients (adapted from [30]).
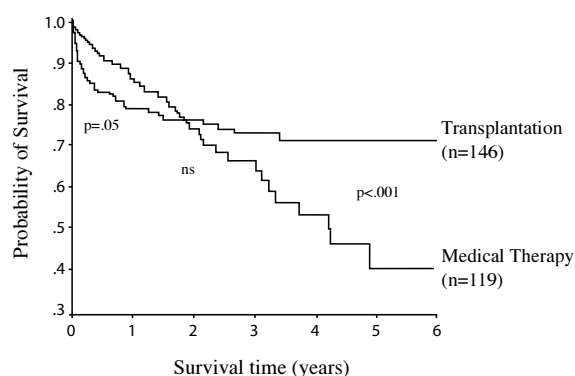
Future therapeutic options

Despite the significant advances in the treatment of end stage heart failure, mortality and morbidity remain high. Thus, various new concepts are being developed and investigated. An incomplete list of promising therapeutic approaches is depicted in table 2. On the one hand, these approaches use completely new therapeutic modalities. On the other hand, they try to modify already existing modalities or to use them in the context of heart failure. For example, treatment of anaemia in heart failure patients may improve symptoms and possibly also prognosis, as suggested by several small recent studies [37, 38]. However, ongoing large scale studies need to be awaited before these therapeutic options can be generally recommended.

In our country, left ventricular assist devices are used nowadays as bridge to transplantation only, but this is likely to change in the future. Possibly, regeneration of the myocardium will be an alternative for replacement of the heart. Mechanically influencing remodelling is another new approach. All these approaches are spectacular and promising, but they also carry substantial risks. Thus, it is still too early to foresee their future place in the therapy of end stage heart failure. Various less spectacular approaches are also under investigation. Since they use targets different from those of current treatment, they may well significantly improve outcome in end stage heart failure. CRT as the most recent new approach impressively showed the potential for further improvements, even in patients on optimal medical therapy [18].

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Table 2

Selection of promising future therapeutic approaches for end stage heart failure.

Mode of action	Therapeutic approach
Regeneration of myocytes	Stem cells, myoblasts, stimulation of endogenous stem cells, gene therapy
Replacement of heart	Permanent assist device, xenotransplantation
Reverse remodelling	Surgical or interventional mitral valve repair / annuloplasty, acorn device
Resynchronisation	CRT as early therapy
Treatment of co-morbidities	Erythropoietin, antianorectic agents, CPAP, A1-agonists
Individualisation	Individually targeted therapies (eg BNP-guided)

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