

Integrated heart failure management in the patient with heart failure caused by left ventricular systolic dysfunction

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Key Points

1. The increasing burden of heart failure is a result of the aging population and improvements in cardiac care. It is estimated that 660,000 new cases of heart failure are diagnosed every year in the United States.
2. Heart failure with normal ejection fraction (HFNEF) is part of a single entity of heart failure that includes also heart failure with decreased ejection fraction. The prognosis of HFNEF is similar to the prognosis of patients with low ejection fraction.
3. Sustained activation of the renin angiotensin aldosterone system as well as the sympathoadrenergic system is one of the main causes of progression of this disease, if not the most important one.
4. ACE (angiotensin converting enzyme) inhibitors result in beneficial effects on hemodynamics, exercise capacity and improve outcomes, reducing the mortality and hospitalizations rates, of the patients with heart failure.
5. Angiotensin receptor blockers (ARBs) are similar beneficial effects as ACE inhibitors so that they are valid alternatives to ACE inhibitors in patients who do not tolerate them. When added to ACE inhibitors, ARBs provide a further improvement in outcomes.
6. Aldosterone antagonists are recommended in patients with severe symptoms of heart failure and reduced left ventricular ejection fraction in addition to ACE inhibitors, beta-blockers and diuretics.
7. Overwhelming evidence supports the long term efficacy of beta blocker therapy on all cause and cardiovascular mortality in patients with mild to severe heart failure.

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8. Hydralazine and isorbide dinitrate are useful for the treatment of heart failure in African-American patients. Treatment with these agents in combination improves symptoms and outcomes.
9. Antiarrhythmic agents are not indicated for sudden cardiac death prophylaxis in heart failure patients.
10. QRS prolongation is an independent predictor of poor prognosis in various heart failure populations.

Introduction

Definitions and epidemiology

Heart failure (HF) has been defined as a syndrome in which a patient has symptoms, typically breathlessness or fatigue, either at rest or during exertion, and/or ankle swelling, and objective evidence of cardiac dysfunction at rest [1].

Heart failure is the final stage of virtually all cardiac diseases and represents a major public health problem for Western countries[1–3]. The prevalence of HF has risen to epidemic levels in both North America and Europe [4]. It is estimated there are approximately 5,300,000 adults with HF in the United States with 660,000 new cases diagnosed every year—these cases have been increasing steadily over the past 20 years [5, 6]. Due to the aging population and the improvement of acute cardiac care, the burden of HF is expected to grow further, with one projection showing an increase in prevalence of HF of 31% and 17%, in males and females, respectively by the year 2020. [7] The number of hospitalizations has also risen—1,084,000 hospital discharges (a 171% increase as compared to 1979) were recorded in 2005 in the United States [4]. Similar data have been obtained in Europe with a prevalence of 0.4–2% of the general European population, which shows acute HF as the main cause of hospitalization in patients >65 years of age [8, 9]. The overall economic cost of HF is expected to reach US\$34.8 billion in 2008 [4] with HF causing 2–3% of the total healthcare expenditure in European countries

Mortality rates have significantly decreased over the last 10 years [10–13]. New drugs and cardiac resynchronization therapy (CRT) have further reduced annual mortality to rates of approximately 8–10% [14–16]. However, the prognosis for patients with HF remains worse in an in-hospital mortality rate of 4–9%, with postdischarge 6-month mortality and rehospitalization rates of 9%–15% and 30–45%. One-year and 5-year mortality rates remain at 20–30% and about 50%, respectively [10–13].

Asymptomatic and symptomatic, systolic and diastolic left ventricular dysfunction

Heart failure is the final outcome of a process initiated by risk factors and, then, a cardiovascular disease causing myocardial damage, followed by left ventricular (LV) remodeling, LV dysfunction, and progression to symptomatic HF [2, 3]. As

a result, the first step of an integrated HF management strategy is prevention with effective treatment of known risk factors (hypertension, diabetes, hyperlipidemia) and early diagnosis and treatment of LV dysfunction in subjects at high risk (e.g. families of patients with dilated cardiomyopathy, patients on chemotherapy) [2, 3]. Either systolic and/or diastolic LV dysfunction or, more frequently, their combination may be the underlying mechanism of HF. Systolic dysfunction is usually defined on the basis of the LV ejection fraction (EF). In general, 38–54% of patients with HF have preserved left ventricular ejection fraction (LVEF) [21]. As these patients may have other, more subtle, abnormalities of LV systolic function (e.g. a depressed LV long-axis shortening) and as abnormalities of diastolic function are present also in the patients with a low LVEF (in whom the abnormalities may actually be more related to symptoms than abnormalities of systolic function), the definition of HF with preserved EF (HFPEF) or HF with normal EF is preferred, over that of diastolic HF [1, 21].

The hypothesis underlying this preferred definition is that HF is a single-entity characterized by a progressive decline in LV systolic performance so that there is a progression from HFPEF to HF with reduced LVEF. Actually, LV volumes, measured by three-dimensional echocardiography, are often increased in HFPEF patients, compared to normal subjects after matching for age, gender, and body size, which suggests an earlier stage of LV remodeling in these patients [21]. In addition, LVEF has shown a unimodal distribution in large studies including HF patients independent of their LVEF values. This definition is in agreement with the “single entity hypothesis” for HFPEF and HF with reduced LVEF [9,22,23]. Lastly, despite demographic differences (HFPEF patients are more likely to be females, older, and with a history of hypertension), the prognosis of HFPEF is similar to the prognosis of the patients with low LVEF with respect of both hospitalization and mortality [21].

Once the diagnosis of HF is established, treatment is aimed at the improvement of symptoms, quality of life, and/or survival [1–3]. Several pharmacological and nonpharmacological tools have consistently been shown to be effective in reducing mortality and morbidity [1–3]. However, treating HF remains an extremely challenging task. We will summarize the optimal medical management of chronic HF. We will focus mainly on patients with evidence of LV systolic dysfunction. There are no major differences in the medical treatment of patients with HFPEF, compared to those with reduced LVEF [24]. We will not discuss the treatment of these patients (HFPEF) or of the patients with acute HF in this chapter.

Medical management of chronic heart failure

General considerations

Medical treatment of HF is based on the combination of different agents administered with the aim of improving prognosis (mainly through neurohormonal

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inhibition) and/or relieving symptoms. Combination of an ACE inhibitor and a beta-blocker constitute the background therapy for virtually all HF patients, the addition of agents, such as angiotensin receptor blockers (ARBs), aldosterone antagonists, hydralazine, and isosorbide dinitrate, may provide, additional survival benefits [1–3]. As a rule, only agents with proven efficacy in large randomized controlled trials are recommended for clinical practice, and these agents should be administered at the doses shown to be effective in controlled trials [1–3]. Failure to reach the target dose may translate into lower clinical benefits or no benefits at all. To be effective, medical therapy of HF with neurohumoral antagonists has to be optimal with regard to drug choice, as well as include up-titration to the recommended dose [1–3]. Other agents are critical in the management of HF not for prognosis but rather for their effect on symptoms. Diuretics are of crucial importance in the control of the volume status and for improving symptoms due to fluid retention and congestion, while digoxin ameliorates the clinical status and reduces the need for hospitalization due to HF [1–3].

Angiotensin converting enzyme inhibitors

The introduction of angiotensin converting enzyme (ACE) inhibitors into clinical practice has radically changed treatment of HF. Their use is based on numerous placebo-controlled trials showing their beneficial effects on outcome [25, 26]. Their effects were also shown to be different and of greater magnitude, with respect to outcome, compared to those of direct vasodilators [27]. Based on these data, ACE inhibitors have become, and still remain, the drugs of first choice for the treatment of chronic HF [1–3]. Their efficacy has also indirectly proven the hypothesis that neurohormonal mechanisms, namely the renin-angiotensin aldosterone system (RAAS), play a pivotal role in the progression of LV dysfunction and the poor outcome of the patients with HF [28–33].

Mechanisms

Sustained activation of the RAAS, as well as of the sympathoadrenergic system, although initially acting as a compensatory mechanism, is a major determinant of the development and progression of HF ultimately leading to LV dysfunction and maladaptive remodeling. Modulation of these neurohormonal systems plays a pivotal role in the management of HF and inhibitors of the RAAS and beta-adrenergic receptor blockers are the keystones of current medical therapy of HF [28–33]. The RAAS is activated in patients with HF and has multiple effects contributing to the progression of this disease [31, 32, 34]. Angiotensin II (AII) causes constriction of the peripheral vasculature with increased LV afterload, is implicated in the development of atherosclerosis, and causes salt and water retention at the renal level. In the long-term, AII stimulation causes hypertrophy of smooth muscle vascular cells, which contributes further to peripheral

vasoconstriction, and myocardial hypertrophy. Myocardial pathological hypertrophy and fibrosis are the mechanisms causing LV remodeling and dysfunction.

In addition, AII stimulates sympathetic drive through increased norepinephrine release from nerve terminals, increased ganglionic transmission, and heightened sympathetic central drive. It also stimulates aldosterone secretion, and aldosterone further contributes to renal salt and water retention, potassium loss, myocardial fibrosis, and increased sympathetic drive.

Clinical effects

Angiotensin converting enzyme inhibitors act upstream in the RAAS inhibiting the conversion of Ang I to Ang II and the degradation of bradykinin [1–3]. It has become clear, however, that ACE inhibitors provide only an incomplete inhibition of the RAAS so that concomitant administration of angiotensin receptor blockers and/or aldosterone antagonists is warranted in many patients with HF [14, 35].

As early as 30 years ago, ACE inhibitors were shown to exert many beneficial effects on hemodynamic parameters and exercise capacity [36, 37]. More importantly, these agents were shown to inhibit or reverse LV remodeling with stable or reduced LV volumes during long-term treatment [38, 39].

The effects on outcomes of long-term therapy with ACE inhibitors have been assessed in several randomized controlled clinical trials in different clinical conditions, including chronic HF [25, 26], postmyocardial infarction HF and/or LV systolic dysfunction [40–43], and asymptomatic LV systolic dysfunction [44] (Table 1.1). In patients with chronic HF, long-term administration of ACE inhibitors is associated with a significant reduction in mortality and hospitalizations for HF [25–27]. In the post-MI setting, ACE inhibition has been shown to favorably affect LV remodeling, reduce HF hospitalizations, as well as recurrent ischemic events, and improve survival [40–43].

The role of ACE inhibitors in patients with asymptomatic LV systolic dysfunction was assessed for the first time in the Studies of Left Ventricular Dysfunction (SOLVD)-Prevention study. This trial included 4,228 patients with asymptomatic LV systolic dysfunction (EF <35%), randomized to enalapril 10 mg b.i.d. or a placebo, and showed a significant reduction in the number of deaths and HF hospitalizations, but not of mortality alone, with the ACE-inhibitor (20% risk reduction; 95% confidence interval [CI], 9–30%; $p < 0.001$) [44]. The lack of effects on mortality alone in the original study is explained by the low number of events. Accordingly, Jong et al. reported an improvement of the 12-year survival in the SOLVD-Prevention study population randomized to enalapril as compared to those on a placebo in a longer-term follow-up [45]. Persistence of the beneficial effects of ACE-inhibitor therapy has been shown also in the 10-year follow-up of the patients randomized in CONSENSUS (risk reduction of 30%, 95% CIs 11–46%; $p = 0.008$). This long-term follow-up study showed that the beneficial effects of enalapril, compared to a placebo, was sustained for at least 4 years

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Table 1.1 Selection of landmark controlled trials of medical therapy in heart failure and asymptomatic and symptomatic left ventricular dysfunction.

	Trial	Agent	Inclusion criteria		Patients No.	Target dose	Follow-up	Overall mortality ⁽⁻⁾
			NYHA Class	LVEF				
ACE-Inhibitors <i>Chronic HF</i>	Captopril Multicenter Research Group	Captopril	II-III	≤40%	92	100 mg t.i.d.	12 weeks	n/a
	CONSENSUS	Enalapril	IV	n/a	253	20 mg b.i.d.	188 days	-40%
	SOLVD-Treatment	Enalapril	II-III	≤35%	2,569	10 mg b.i.d.	41.4 months	-16%
	SAVE	Captopril	-	≤40%	2,231	25-50 mg t.i.d.	42 months	-19%
	AIRE	Ramipril	Clinical HF	-	2,006	5 mg b.i.d.	15 months	-27%
	TRACE	Trandolapril	-	≤35%	1,749	4 mg s.i.d.	24-50 months	-22%
<i>Asymptomatic LV dysfunction</i>	SOLVD-Prevention	Enalapril	-	<35%	4,228	10 mg b.i.d.	37.4 months	N.S.
ARBs <i>Chronic HF</i>	CHARM-Added	Candesartan	II-IV	≤40%	2,548	32 mg s.i.d.	41 months	N.S.
	CHARM-Alternative	Candesartan	-	≤40%	2,028	32 mg s.i.d.	33.7 months	-23%*
	VALIANT	Valsartan vs. Captopril	-	<40%	14,703	320 mg s.i.d. vs. 80 mg t.i.d.	24.7 months	noninferiority

Aldosterone Antagonists									
Chronic HF Post-MI	RALES	Spirolactone	III-IV	≤35%	1,633	25 s.i.d.	24 months	-30%	
	EPHESUS	Eplerenone	-	≤40%	6,632	50 mg s.i.d.	16 months	-15%*	
Beta-Blockers Chronic HF Post-MI	US Carvedilol Heart Failure Study	Carvedilol	II-IV	<35%	1,094	25-50 mg b.i.d.	7 months	-65%	
	CIBIS II	Bisoprolol	III-IV	<35%	2,647	10 mg s.i.d.	15.6 months	-34%	
	MERIT-HF	Metoprolol CR/XL	II-IV	<40%	3,991	200 mg s.i.d.	15 months	-34%	
	COPERNICUS	Carvedilol	III-IV	<25%	2,289	25 mg b.i.d.	10.4 months	-35%	
	CAPRICORN	Capricorn	-	≤40%	1,959	25 mg b.i.d.		-23%	

* cardiovascular death or hospital admission for HF. ACE = angiotensin converting enzyme; AIRE = Acute Infarction Ramipril Efficacy; ARBs = angiotensin receptor blockers; CAPRICORN = Carvedilol Post Infarct Survival Control in Left Ventricular Dysfunction; CHARM = Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity; CIBIS = Cardiac Insufficiency Bisoprolol Trial; CONSENSUS = Cooperative North Scandinavian Enalapril Survival Study; COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival; EF = ejection fraction; EPHESUS = Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; HF = heart failure; MERIT = Metoprolol Controlled-Release Randomized Intervention Trial in Congestive Heart Failure; MI = myocardial infarction NYHA = New York Heart Association; RALES = Randomized Aldactone Evaluation Study; SAVE = Survival and Ventricular Enlargement; SOLVD = Studies of Left Ventricular Dysfunction; TRACE = Trandolapril Cardiac Evaluation; VALIANT = Valsartan in Acute Myocardial Infarction Trial.
(-) a reduction in overall mortality of (minus)...

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with a 50% average prolongation of life duration (from 521 days to 781 days) [46]. These data, therefore, also show that the beneficial effects of ACE inhibition are limited in time, and ACE inhibitors cannot be considered the only treatment of patients with chronic HF both with respect to inhibition of the RAAS and, more generally, with the aim of improving outcomes.

Recommendations for clinical practice

All current guidelines recommend the use of an ACE inhibitor as first-line therapy for all patients with reduced LVEF (≤ 40 –45%) with or without current or prior symptoms of HF. Doses of ACE inhibitors indicated for the treatment of HF (i.e. captopril, enalapril, lisinopril, ramipril, and trandolapril) should be those that have been shown to be effective in clinical trials [1–3].

Angiotensin receptor blockers

Angiotensin receptors blockers (ARBs) block the action of AII on AII type I receptors (AT1) [1, 2, 14, 47]. ARBs do not interfere with the degradation of bradykinin as ACE inhibitors do. ARBs are different than ACE inhibitors in two ways: first, lack of the favorable effects of increased kinin levels on peripheral vasodilation and LV remodeling; second, lack of the kinin-mediated side effects of ACE inhibitors, namely, cough and angioneurotic edema. In addition, administration of ARBs is associated with increased AII levels with greater stimulation of AII type II receptors, which seem to mediate mainly beneficial effects on peripheral vasodilation and myocardial hypertrophy.

Clinical effects

The hemodynamic and antiremodeling effects of ARBs are similar to those of ACE inhibitors [48]. A II levels tend to progressively increase after months to years of ACE-inhibition therapy [35] (the so-called escape phenomenon) and, as a consequence, the effects of ACE inhibitors on cardiac remodeling attenuate after 1 year of treatment. These observations, along with the biologic rationale of a more complete inhibition of the RAAS, have led to the development of strategies combining the use of ARBs and ACE inhibitors.

Clinical trials

Trials have been specifically designed to assess the effects of candesartan, losartan, and valsartan, the only ARBs currently recommended for use in HF patients, as alternatives to [49–52], or in combination with, [53–55] ACE inhibitors.

Among the trials in patients with post-MI LV systolic dysfunction or HF, Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan (OPTIMAAL) showed similar effects on outcomes of losartan, compared to captopril. The Valsartan in Acute Myocardial Infarction (VALIANT) trial demonstrated the noninferiority of valsartan, compared to captopril, with respect to

all-cause mortality, the combined cardiovascular endpoints, and all of the secondary endpoints [49].

In the Valsartan in Heart Failure Trial (Val-HeFT) trial, 5,010 patients with chronic HF were randomized to valsartan, titrated up to dosage of 160 mg b.i.d., or a placebo, on top of optimal medical treatment for HF, including ACE inhibitors in 93% of patients and beta-blockers in 35% of patients [54]. Candesartan administration was associated with a reduction in the primary endpoint of morbidity and mortality and in HF hospitalization but not a reduction in mortality alone [54]. In the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM)-Added trial, 2,548 patients with NYHA Class II–IV HF and LV dysfunction (EF < 40%) already treated with ACE inhibitors (all patients), beta-blockers (55%), and aldosterone antagonists (17%) were randomized to a candesartan 32 mg, once daily dosage, or a placebo. Addition of candesartan reduced the incidence of the primary endpoint (risk reduction, 15%, 95% CIs, 4–15%; $p = 0.011$), as well as its individual components: cardiovascular deaths ($p = 0.029$) and HF hospitalizations ($p = 0.014$) [55]. An important result showed that the association of ACE inhibitors and ARBs in patients on beta-blockers and/or on high doses of ACE inhibitors was associated with a reduction in cardiac events. These results differ from the results in the Val-HeFT [54, 55]. These differences are likely explained by the larger number of patients on beta-blocker treatment and by greater severity of HF in the patients who were randomized in the CHARM trial compared to those in Val-HeFT (e.g. patients in Class II randomized in the CHARM-Added trial had to have hospital admission for a cardiac reason in the previous 6 months, more patients were on beta-blockers, and the event rate was higher).

The CHARM-Alternative trial specifically tested the hypothesis of the efficacy of ARBs as an alternative to ACE-inhibitor-intolerant patients [52]. Among the 2,028 patients enrolled in the study, treatment with a candesartan 32 mg daily dosage was associated with a significant reduction of cardiovascular mortality and HF hospitalizations as compared to placebo (unadjusted risk reduction 23%; 95% CI, 11–33%; $p < 0.0004$; covariate adjusted risk reduction 30%; 95% CI, 19–40%; $p < 0.0001$), with similar discontinuation rates compared to placebo (30% vs. 29%). Similar effects were also found with respect to clinical endpoints [52]. Consistently with what was shown by a retrospective analysis of Val-HeFT [56], the magnitude of the beneficial effects of ARBs administration, compared to a placebo, were larger than when these agents are added to ongoing ACE-inhibitor treatment.

Recommendations for clinical practice

ARBs of proven efficacy in HF trials is recommended as a first-line therapy in patients intolerant to ACE inhibitors. An association of ARBs and ACE inhibitors appears reasonable in patients with reduced LVEF who remain symptomatic despite background treatment with conventional agents [1–3,57].

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Aldosterone antagonists

Activation of the RAAS causes an increase in plasma aldosterone levels. These remain elevated despite treatment with ACE inhibitors and/or ARBs (aldosterone escape phenomenon) [35,58]. Aldosterone has many untoward effects including salt and water retention, increased potassium loss with hypokalemia, increased sympathetic drive, myocardial hypertrophy, and fibrosis. These changes are consistent with the increase in cardiovascular events in the patients with higher aldosterone plasma levels [59–61] and constitute the rationale for concomitant administration of aldosterone receptor blockers in patients with HF on optimal medical therapy. This hypothesis has been formally tested in the Randomized Aldactone Evaluation Study (RALES) [62] and the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) trials [63].

The RALES trial assessed the effects of a spironolactone 25 mg daily dosage, as an adjunct to ACE inhibitors and diuretics, in 1,633 patients with severe HF (LVEF <35% and NYHA Class IV or Class III but Class IV in the previous 6 months). Spironolactone treatment was associated with a 30% (95% CI, 18–40%; $p < 0.001$) relative risk reduction in mortality and a 35% risk reduction (95% CI, 33–46%; $p < 0.001$) in HF hospitalizations paralleled by an improvement in functional class [62]. The selective aldosterone antagonist eplerenone was evaluated in the EPHESUS trial in 6,632 patients with recent MI, LV systolic dysfunction, and either symptomatic HF or diabetes. Therapy with an eplerenone 50 mg daily dosage resulted in a 15% reduction in all-cause mortality (95% CI, 4–25%; $p = 0.008$), with a significant reduction in cardiovascular death (including sudden death), and in hospitalizations for HF and cardiovascular causes [63].

Recommendations for clinical practice

Administration of an aldosterone antagonist is recommended in patients with severe symptoms of HF (NYHA Class III–IV) and reduced LVEF in addition to ACE inhibitors, beta-blockers, and diuretics. The adjunct of these agents is also recommended in post-MI patients with evidence of LV systolic dysfunction and HF. Careful monitoring of serum potassium and creatinine is necessary [1–3, 57]. Current guidelines do not give any indication with respect to which drug (e.g. an ARB or an aldosterone antagonist) should be added first when a patient is still symptomatic and is still receiving on ongoing treatment with ACE inhibitors and beta-blockers [1–3].

Quadruple combination of neurohormonal antagonists

Although fascinating from a biologic standpoint, a complete inhibition of the RAAS with a combination of ACE inhibitors, ARBs, and aldosterone antagonists, on top of beta-blockers, is used infrequently because of its low tolerability. A retrospective analysis from the CHARM trials has, however, shown no change in the beneficial effects on outcomes with candesartan, compared to a placebo,

when added to triple therapy with neurohormonal antagonists, including ACE inhibitors, aldosterone antagonists, and beta-blockers, compared to the results in the overall study population [64]. Increased risk of hypotension, renal dysfunction and hyperkalemia must, however, be taken into account when administering all four neurohormonal antagonists [1–3, 20, 57].

Beta-blockers

Sympathoadrenergic stimulation has long-term untoward effects on the failing heart. These include beta-1 receptor downregulation and desensitization, increased heart rate, increased wall stress and myocardial oxygen consumption, abnormal sarcoplasmic reticulum calcium cycling, induction of fetal gene program with downregulation of alpha-myosin heavy chains and upregulation of beta-myosin heavy expression with decreased myosin ATPase enzyme velocity, and slow speed of contraction, induction of cell necrosis and apoptosis [30, 33, 65–68]. These mechanisms constitute the rationale basis for beta-blocker treatment of patients with HF.

Effects on LV function and symptoms

Beta-blocker administration has short-term negative inotropic effects. For many years, this has represented a contraindication to their administration to patients with HF. However, it may be safely avoided by starting treatment with very low doses followed by their gradual and slow up-titration to target doses [1–3, 57, 69]. In selected patients with severe and hemodynamically unstable HF, concomitant administration of inotropic agents acting independently from beta-receptors may be useful [8, 70].

Long-term therapy with beta-blockers produces an increase in stroke volume and cardiac output along with a reduction in pulmonary capillary wedge pressure, right atrial pressure, and systemic vascular resistance [71–73]. These favorable hemodynamic changes are generally not associated with significant improvement in exercise capacity because blunting of the heart rate response to exercise does not allow a sufficient increase in exercise cardiac output. An improvement in symptoms may be more easily shown by direct patient assessment, questionnaires, and, above all, in single center studies by submaximal exercise capacity assessment [74,75]. An exception may be represented by nebivolol, as shown in a study in patients with HF and preserved LVEF [76].

All of the beta-blockers currently approved for the treatment of HF, have been shown to induce a significant improvement in cardiac function and a true global and structural reverse remodeling of the LV [77–79]. The profound changes in LV structure and function associated with beta-blocker therapy (more elliptical shape of the LV, reduction in mitral regurgitation and LV volumes) show the importance of sympathetic activation in the pathogenesis of myocardial dysfunction and the ability of beta-blockers to interfere with the intrinsic mechanisms leading to HF [65, 66, 80]. The observed benefits on LV function, as well

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as those on outcomes, are maintained or magnified over time and are superior to those obtained with any other agent available for treating HF [65, 66].

Nonischemic aetiology of HF, higher blood pressure, and reversible contractile dysfunction at dobutamine echocardiography (as indexes of reversibility of myocardial damage) are predictors of greater improvement in LVEF and function during long-term beta-blocker therapy [81, 82]. Marked improvement in LVEF may be observed in approximately 25% of patients with chronic HF and is associated with an excellent long-term outcome [81]. Beta-blockers were the first agents for which such a tight link between improvement in LV function and outcome could be shown. Similar results were going to be later shown with CRT [83–85].

Effects on outcomes

There is overwhelming evidence supporting the beneficial effects of long-term beta-blocker therapy on all-cause and cardiovascular mortality as well as all-cause, cardiovascular, and HF hospitalizations. These beneficial effects have been shown across a broad range of severity of LV systolic dysfunction and NYHA classes [86–90]. The reduction in mortality with beta-blockers, compared to placebo, is about 35% and is greater in magnitude compared to that obtained with other neurohormonal antagonists [65]. There is also a significant percent reduction in sudden death (41–44%), all-cause hospitalizations (18–20%) and HF hospitalizations (32–35%) [86–90].

Differences between beta-blockers with respect to their effects on outcome, consistent with what has been previously shown with respect to their effects on LV function [67, 73], have been shown [91]. Although differences in doses and degrees of beta-blockade may have influenced these results [92], it is likely that peculiar characteristics of carvedilol (as compared to metoprolol tartrate), yield a more stable and persistent blockade of beta-1 adrenergic receptors [70, 93], and have ancillary effects on other mechanisms (beta-2 receptor blockade, antioxidant activity, metabolic effects, protection from ischemic events), which may account for differences in outcomes [94–96].

The efficacy of beta-blockers has been more recently shown in groups of patients that were not included in the initial trials. The Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN) study showed the beneficial effects on mortality of carvedilol in patients with post-MI LV dysfunction on optimal medical treatment including ACE inhibition and reperfusion [97]. The recent Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENIORS) pointed out the potential effects of beta-blockade therapy in elderly patients (≥ 70 years) with a broad spectrum of LV systolic dysfunction. [98] This trial included 2,128 patients with a mean age of 76 years, history of HF regardless of LVEF, who were randomized to either nebivolol (target dose 10 mg) or placebo. Patients were followed for a mean of 21 months [98]. Nebivolol was associated with a 14% relative risk

reduction (95% CI 1–%; $p = 0.039$) for the occurrence of the primary endpoint of all-cause mortality and cardiovascular hospitalizations [98]. To overcome the potential bias, due to the differences in the studied populations and compare to previous HF trials, a non-prespecified analysis of a subgroup of patients aged <75 years and with LVEF $\leq 35\%$ was performed. In this subgroup of patients, more similar to those from the other major mortality trials, there was a 27% (95% CI, 4–44%) relative risk reduction for the primary endpoint and a 38% (95% CI, 11–37%) relative risk reduction for all-cause mortality alone [98], which is similar to that found in previous HF trials.

It has been recently proposed that, at least with some beta-blockers (e.g. bucindolol), assessment of gene polymorphisms may help to better select patients more likely to show a favorable response to treatment. The influence of polymorphisms of the genes encoding for the beta-1 adrenergic receptors was assessed in 1,040 patients enrolled in the Beta-Blocker Evaluation of Survival Trial (BEST). Bucindolol had a neutral effect on mortality compared to placebo, in this trial. However, homozygotes for the Arg-389 allele, associated with a three-fold increase in sensitivity to adrenergic stimulation *in vitro*, had an age-adjusted, sex-adjusted, and race-adjusted 38% reduction in mortality ($p = 0.03$) and 34% reduction in mortality or hospitalization ($p = 0.004$) when randomized to bucindolol versus a placebo. In contrast, Gly-389 carriers had no clinical response to bucindolol compared with the placebo [99].

Recommendations for clinical practice

Bisoprolol, carvedilol, and sustained release metoprolol succinate, are recommended for the treatment of all patients with mild-to-severe HF and reduced LVEF [1–3,57]. European guidelines include also nebivolol among the beta-blockers indicated for HF treatment [1]. Beta-blockers should always be used in association with ACE inhibitors (although the recent CIBIS-III trial showed no difference in outcomes when beta-blockers are started first) [100]. As mentioned earlier, beta-blockade therapy should be initiated with very low doses followed by gradual titration up to doses achieved in clinical trials. Doses are shown in the guidelines [1–3,57]. If possible, beta-blockers should not be discontinued in patients with acute decompensation of HF as this may be associated with increased mortality [8, 101].

Diuretics

Fluid retention, with systemic and/or pulmonary congestion, accounts for the vast majority of symptoms in HF patients [102, 103]. Diuretics are, therefore, the mainstay of treatment of symptoms of the patients with HF. Diuretics promote the urinary excretion of salt and water by acting at different levels in the nephron: the Henle loop for loop diuretics (furosemide, torasemide, bumetanide, etacrinic acid) and the distal convoluting tubule for thiazides, metolazone and potassium-sparing diuretics [102, 104]. Loop diuretics are the preferred agents for most of

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the patients with the possible exception of only patients with mild symptoms [1, 2].

Diuretics promptly ameliorate symptoms, reduce signs of congestion, and treat and prevent salt and water retention[1–3]. Their effect on symptoms has always prevented any randomized controlled trial to assess their effects on outcomes. However, diuretic therapy [105–107], as well as treatment with high furosemide doses [108, 109], have been associated with a poor outcome (mortality, hospitalizations, incidence of worsening renal function). These associations persist after adjustment for other baseline variables, including those related to HF severity. This suggests, although it does not prove, that diuretic treatment may contribute to the progression of LV dysfunction and HF [110]. The potential mechanisms that may be involved include neurohormonal activation, namely RAAS [111], electrolyte abnormalities (with increased arrhythmic risk) [105, 106, 112], and worsening renal function [109]. Long-term treatment with loop diuretics is also associated with the development of resistance (e.g. the need of increasing doses to achieve diuresis and the increase of maximal diuretic response). This is a hallmark of advanced HF and one of the major problems in these patients [20].

Concerns regarding the long-term effects of diuretic therapy have fostered research to look for potential alternatives (e.g. ultrafiltration) [113] or concomitant agents (e.g. adenosine antagonists, RAAS inhibitors) [114], which may counteract the untoward effects of diuretic treatment. To date, it is universally recommended to administer diuretics at the lowest doses that are effective to correct and prevent salt and water retention and combine them with ACE inhibitors and beta-blockers[1–3].

Digitalis

Cardiac glycosides are among the oldest medications still used in current medical practice. Digitalis exerts positive inotropic effects via inhibition of Na-K-ATPase and stimulation of Na⁺-Ca²⁺ exchange with a secondary increase in intracellular calcium [115]. Furthermore, digitalis modulates the autonomic nervous system activity by partially restoring the responsiveness of the baroreflex system, possibly at blood concentrations lower than those necessary to achieve an inotropic effect [115]. Digitalis is useful for symptom control as it may improve clinical status and exercise tolerance, and decrease HF hospitalization rate. No effect on mortality has been shown in the same large multicenter trial in the overall study group [116]. Retrospective analyses of the Digitalis Investigators Study have shown opposite effects on mortality depending on the serum digoxin levels achieved during treatment. Mortality was reduced with digoxin, compared to a placebo, only in the patients who achieved low serum digoxin concentration (SDC) (0.5–0.9 pg/ml) during treatment whereas HF hospitalizations were reduced independently from SDC [117]. Similar results were obtained in a

previous analysis, which also showed an increase in mortality in the patients with SDC >1.2 ng/ml [118].

Recommendations for clinical practice

Digitalis glycosides can be recommended for the prevention of HF hospitalizations in the patients with HF and severe, NYHA Class III–IV, HF and/or previous HF hospitalizations. It should be administered at low doses targeting SDC less than 1 ng/ml. Digitalis remains indicated in the patients with HF and atrial fibrillation for heart rate control [1].

Hydralazine-isosorbide dinitrate

Vasodilating agents, such as isosorbide dinitrate, theoretically could be useful in the treatment of chronic HF as they may improve dyspnea through a reduction in LV preload [119]. The association of hydralazine and isosorbide dinitrate has been shown to be less effective in improving outcomes, compared to enalapril therapy [27]. However, it has been more recently shown to further improve outcome, compared to a placebo, in African-American patients already treated with neurohormonal antagonists [120]. Accordingly this association is indicated in the HFSA guidelines as part of standard therapy in African-Americans with reduced LVEF [3]. This combination may be useful for symptomatic treatment in patients with LV systolic dysfunction persistently symptomatic despite optimal therapy.

Antiarrhythmic agents

The use of antiarrhythmic agents for the prevention of sudden cardiac death has been investigated in several randomized controlled trials. The results of these studies have led to the absolute contraindication to the use of Class I antiarrhythmic drugs and d-sotalol because of a significant increase in mortality associated with administration of these agents [121, 122]. Amiodarone and dofetilide have been shown to exert neutral effects on overall mortality and sudden cardiac death so that their administration for primary prevention of sudden cardiac death prophylaxis is not recommended [1–3].

Statins

Statins have a plethora of nonlipid-lowering properties that are, theoretically, useful for the treatment of HF. Evidence from experimental and observational studies suggest that statin therapy may improve cardiac function and LV remodeling along with clinical status mainly through modulation of the systemic inflammatory process [123, 124]. The Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) investigated the effects of rosuvastatin added on top of optimal medical therapy in elderly patients with ischemic systolic HF [125]. Rosuvastatin had a neutral effect on the primary composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, and

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nonfatal stroke ($p = 0.12$). However, patients in the rosuvastatin group had lower all-cause ($p < 0.001$) and HF ($p = 0.01$) hospitalizations rate. The GISSI-HF trial, including patients with ischemic and nonischemic HF, will study the effects of rosuvastatin treatment on outcomes in HF [126].

Disease management programs

Disease management has been initially defined as “a comprehensive, integrated system for managing patients by using best practices, clinical practice improvement and other resources and tools to reduce overall cost and improve measurable outcomes in the quality of care” [127]. Disease management programs encompass three major levels of intervention: HF clinics, in which assistance is provided essentially in an outpatient clinic home-delivered care services, and telemedicine [128]. Available evidence on disease management programs suggests that such models of care may significantly reduce hospital re-admission rates and costs while improving patients’ clinical status and quality of life with a positive effect on overall survival [128, 129].

From medical treatment to devices: The role of dyssynchrony in heart failure outcomes

Current medical treatment has allowed an impressive improvement in the natural history of HF caused by LV systolic dysfunction. However, as outlined in the introductory section, the quality of life and prognosis of patients with HF remains poor. Despite the benefits obtained with RAAS inhibitors and beta-blockers, the neurohormonal model of HF has not worked out as expected when other agents, acting on seemingly important mechanisms, have been tested [130]. The current model of multicenter randomized controlled trials (e.g. large trials targeting the widest study group as possible, with a single new treatment added on top of a more-and-more complex pharmacologic therapy, and with no knowledge of the main pathogenetic mechanisms acting in that single patient) seems to have reached its limits. Thus, the poor prognosis and quality of life of HF patients, the failure of the neurohormonal model with the new agents tested, and the failure of recent multicenter trials targeting a noncharacterized HF population have paved the way to device therapy, namely, CRT. This treatment, differently from neurohormonal antagonists, acts on a specific well characterized mechanical defect leading to LV remodeling and HF. The selection of patients based on a simple criterion (e.g. QRS duration) and its direct correction through a device, (e.g. without some of the limitations of medical treatment (pharmacokinetics variability, need of compliance, etc)) may explain the success of this treatment, which is, actually, the most beneficial treatment recently shown for patients with HF.

The presence of a QRS duration > 120 ms on the surface electrocardiogram (ECG) is an index of mechanical dyssynchrony [131]. Although this association

is not absolute, it is estimated that approximately 70% of patients with left-sided conduction delay have evidence of mechanical dyssynchrony [132]. The delay in LV electrical activation causing prolonged QRS duration has an important pathophysiological significance because it is associated to an abnormal and mechanically disadvantageous pattern of LV contraction with an impairment of LV pump performance and increased severity of mitral regurgitation [133]. These changes are consistent with the prognostic significance of QRS prolongation as well as with the beneficial effects of CRT on symptoms and prognosis of the HF patients with LV conduction delay.

Epidemiology and prognosis

A prolongation of the QRS complex, defined as a duration ≥ 120 ms, has been shown in 14–47% of patients with HF, with proportions close to 30% in most studies [134–137]. Intraventricular conduction delay with left bundle branch block (LBBB) morphology is five-fold to seven-fold more frequent than right bundle branch block (RBBB) [137]. QRS prolongation is directly correlated with LV end-diastolic and end-systolic volumes and hence severity of LV dysfunction (Figure 1.1) [138–140]. A QRS duration >120 ms has been shown to have a 99% specificity for LV dysfunction [141]. QRS prolongation is also related with severity of symptoms as assessed through the NYHA functional class [142, 143]. In contrast, it is not related to other factors, such as etiology of HF or concomitant medication. Longitudinal studies have also shown a progressive prolongation of QRS duration during long-term follow-up in HF patients [144].

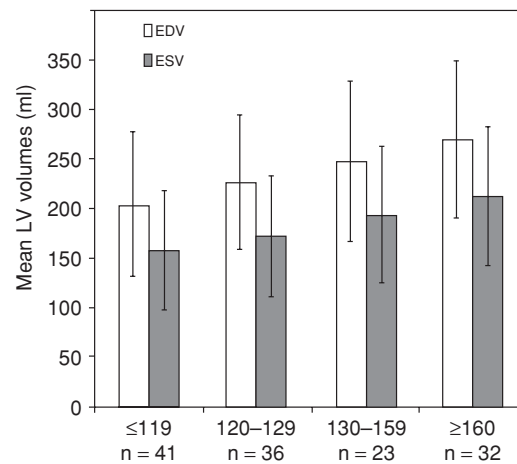


Fig. 1.1 Relationship between QRS duration and left ventricular volumes. A significant increase in LV endiastolic (EDV) and endsystolic (ESV) volumes is noted according to QRS duration. De Winter et al. *Eur J Heart Fail.* 2006;8:275–77.

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QRS prolongation has been identified as an independent predictor of poor prognosis in various HF populations [137]. Its potential role was first proposed in the early 1960s [145]. Further studies have shown that QRS prolongation is associated with a higher risk of all-cause death and sudden cardiac death [134–137]. Iuliano et al. [134] retrospectively analyzed data from 669 patients with HF secondary to ischemic and nonischemic cardiomyopathy subdivided into two groups according to QRS duration [134]. Over the course of a median follow-up of 45 months, 129 deaths (34%) and 143 deaths (49.3%) occurred in patients with QRS <120 ms and in patients with QRS \geq 120 ms, respectively [134]. Sudden death occurred in 17.4% of patients with QRS <120 ms as compared to 24.8% in patients with QRS \geq 120 [134]. The role of QRS prolongation was additive to that of LVEF (Figure 1.2) [134]. A recent subgroup analysis from the Val-HeFT trial confirmed the prognostic impact of QRS widening, indicating a gradual increase in mortality rate with increasing duration of QRS, with a 1.8% mortality rate in patients with a QRS <120 ms, 8% in patients with a QRS duration of 120–159 ms, and 17% in patients with a QRS duration \geq 160 ms during a median observation

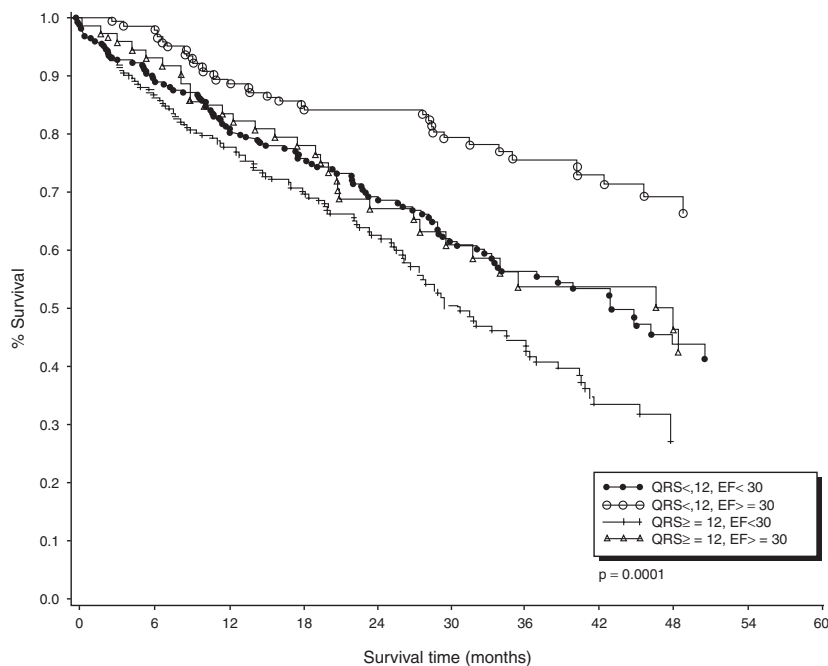


Fig. 1.2 Kaplan-Meier estimates for overall survival on the basis of degree of left ventricular dysfunction and QRS Duration. Among the four groups, patients with both severe cardiomyopathy (EF <30%) and QRS prolongation (>120 ms) have a significant increase in overall mortality. Iuliano S et al. *Am Heart J.* 2002;143:1085-91.

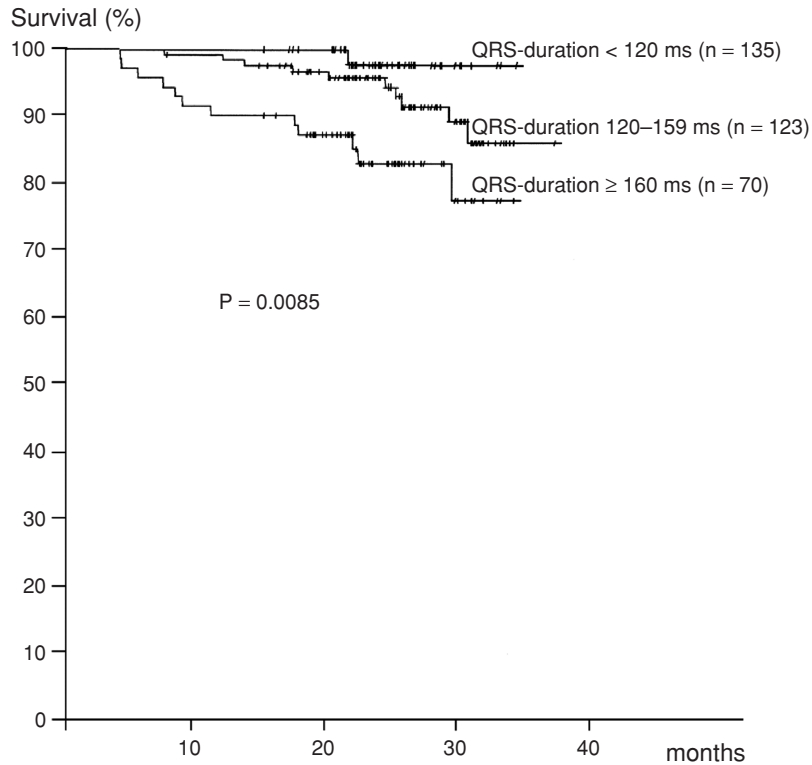


Fig. 1.3 Kaplan-Meier survival curves of patients categorized according to QRS duration <120 ms, 120–159 ms and ≥160 ms. Hofmann M et al. *J Card Fail.* 2005;7:523–8.

period of 25.8 ± 5 months [146] (Figure 1.3). Prolonged QRS duration has been shown to be related to prognosis with a two-fold increase in mortality in patients with a prolonged QRS admitted for acutely decompensated HF [147].

Cardiac resynchronization therapy

A device able to perform atrial-synchronized biventricular pacing (e.g. CRT) was first successfully implanted by Cazeau in 1994, in a 54-year-old man with NYHA Class IV HF and QRS duration of 200 ms [148]. The clinical status of the patient dramatically improved in the first 6 weeks postimplantation. Following this initial experience, the effects of CRT have been extensively investigated in many observational studies and several randomized controlled trials for a total of approximately 15,000 patients with HF and LV systolic dysfunction [149]. Inclusion criteria in major clinical trials of CRT were NYHA Class III–IV, sinus rhythm, QRS duration ≥ 120 ms and LVEF $\leq 35\%$ [149]. A recent systematic meta-analysis of 14 randomized controlled trials indicated that CRT

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improves LVEF (weighted mean difference, 3.0%; 95% CI, 0.9%–5.1%), quality of life (weighted mean reduction in Minnesota Living With Heart Failure Questionnaire, 8.0 points; 95% CI, 5.6–10.4 points), and functional status (improvements of ≥ 1 NYHA class were observed in 59% of CRT recipients in the randomized trials) [149]. More importantly, CRT is associated with a significant reduction in hospitalizations by 37% (95% CI, 7–57%), and in all-cause mortality by 22% (95% CI, 9%–33%) [149]. The positive impact of CRT on morbidity and mortality in HF patients is additional to that provided by polypharmacy as it has been demonstrated in subjects already treated with optimal evidence-based medical therapy [149]. Based on this compelling evidence of the beneficial effects of CRT, current international guidelines recommend the implantation of a CRT, alone or in combination with an implantable cardioverter defibrillator (ICD), device in all eligible HF patients. Accordingly, subjects with persistently symptomatic HF, NYHA functional Class III or ambulatory Class IV, in spite of optimal medical therapy, sinus rhythm, severe LV systolic function ($EF \leq 35\%$), and QRS duration ≥ 120 ms should be implanted with a biventricular pacemaker. It is estimated that approximately 1–3% of all patients discharged alive after their index HF hospitalization, and 15–20% of patients observed in dedicated HF clinics meet CRT trials' eligibility criteria [150], while approximately 50% of these subjects also met trials' eligibility criteria for an ICD [151].

Conclusions

Effective options are now available for the treatment of HF patients. However, despite recent advances in pharmacological and nonpharmacological therapy, morbidity and mortality of HF patients remain unacceptably high [2]. Thus, any effort is necessary to optimize treatment of our patients. Nowadays, this requires an integrated management approach combining medical treatment and devices. On the other hand, the benefits of device treatment have been shown on top of optimal medical management. Such a complex management can not be afforded by a single expert but rather requires the integrated effort of a well-organized team, able to furnish thorough diagnostic assessment, medical therapy, device implantation, and in-hospital and out-of-hospital patient's monitoring, treatment, and follow-up.

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