The impaired left ventricular emptying that characterizes heart failure may result from a variety of cardiac diseases, including myocardial ischaemia or infarction (that alters regional function), cardiomyopathies (that alter global function), and pressure or overload states (that lead to hypertrophy and dilatation of the chamber). This functional abnormality of the left ventricle is an important contributor to symptoms of heart failure and plays a critical role in the sodium retention that leads to congestion in the pulmonary circulation and oedema in the systemic circulation. Consequently, efforts to enhance the contractile force of the left ventricle have characterized strategies for the management of heart failure for the past generation.

The syndrome of heart failure results from various cardiovascular disorders and is characterized by systolic and or diastolic dysfunction. Although central haemodynamic abnormalities are by definition the initiating pathological event in this syndrome, it has been shown that the degree of left ventricular dysfunction does not correlate with exercise tolerance or symptoms. This can be explained, in part, by the complex interplay between central haemodynamic, pulmonary factors and peripheral circulation, as well as by neuroendocrine adaptation. The most frequent symptom of heart failure is exercise intolerance associated with dyspnoea and fatigue upon exertion. Heart failure is associated with high morbidity and mortality. Annual mortality rates of 20-40% have been reported for systolic dysfunction and 10-20% for diastolic dysfunction, depending on the severity of the disease.

Heart failure is characterized by a number of neurohormonal abnormalities. These include: the sympathetic nervous system, as indicated by an elevated plasma norepinephrine lever, the renin-angiotensin system, as identified by an increase in plasma renin activity, increased plasma level of aldosterone; increased activity of the endothelin system with increased plasma levels of big endothelium as well as ET-1, increased activity of cytokines as shown by an increase in TNFa, increased arginine vasopressin levels and probably other systems not fully elucidated. Although not all of these systems have fully studied in terms of their role in remodeling and the efficacy of their inhibition, growing evidence supports a potential direct contribution of norepinephrine, angiotensin II, aldosterone, endothelin and TNFa in the progressive structural process.

The association between elevation of circulating effector hormones of the renin-angiotensin aldosterone system (RAAS) and the progression of congestive heart failure is now irrefutable. In keeping with this, angiotensin-converting enzyme (ACE) inhibitors have been shown to be effective in reducing the incidence of hospitalization and the rate of mortality in patients with systolic left ventricular dysfunction.

Practical aspects of treatment of systolic and diastolic dysfunction

In general, heart failure therapy implies treatment of systolic dysfunction. However, it is expected that diastolic dysfunction (typically a heart disease of the elderly hypertensive) will receive greater attention in the future. Nonetheless, clinicians must clearly understand how the therapy for systolic and diastolic dysfunction in heart failure differs. The various approaches to heart failure management are outlined:

In patients with dyspnoea and pulmonary congestion, diuretics remain the initial agents. Once these congestive symptoms have ameliorated, an ACE-inhibitor or an ß-II blocker should be added to improve cardiac function by reducing afterload and blocking neurohormonal stimulation. Spironolactone

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should be added not for its diuretic but for its beneficial effect on cardiac remodelling and reducing the collagen content of the heart, which may improve diastolic dysfunction. The RALES (Randomized Aldactone Evaluation Study) trial has recently demonstrated the short and long term benefit of spironolactone in patients with severe heart failure. Patients treated with spironolactone and standard therapy, which included ACE-inhibitors and diuretics showed a 30% reduction of mortality over a 2-year period. In the RALES trial, selection criteria required patients to have a history of NYHA class IV heart failure and a left ventricular ejection fraction <=35% within the 6 months prior to enrollment. At the time of randomization the patients were in either class III or IV heart failure, while maintained on standard therapy (an ACE-inhibitor, if tolerated, and a loop diuretics with or without digoxin). The dose of spironolactone was chosen on the basis of a prior carefully performed parallel dose-finding study in which it was shown that 25mg of spironolactone was pharmacologically effective and didn't result in significant hyperkalaemia.

The investigators were allowed to reduce the dose of study medication to 25mg every other day if they saw any tendency toward hyperkalaemia. If, however, after eight weeks there was no evidence of hyperkalaemia but there was evidence of progressive heart failure, the doses of study medication could be increased to 50mg daily. The patients in this trial were to have been followed for three years with the end-point of total all-cause mortality. However, the trial was prematurely stopped at the end of a two year mean follow-up because the data safety Monitoring Committee found that there was a significant mortality benefit in patients who were randomized to spironolactone. Beta-blockers have shown to improve symptomatology and reduce mortality. In severely symptomatic patients; however, "start low, go slow" should be considered.

The next step is to add digitalis, which does not reduce mortality but improves symptoms and reduces the rate of hospitalization. It should be noted that digitalis is particularly indicated in patients with systolic dysfunction who remain symptomatic. Digitalis is not indicated in patients with diastolic dysfunction, except for rate control in the presence of atrial fibrillation.

The second cornerstone in heart failure therapy is the use of beta-blocker. These agents have profound and important effects on survival of patients with systolic dysfunction. However, it is unclear whether patients with diastolic dysfunction experience a beneficial effect. In patients with coronary artery disease beta-blockers improve function by reducing heart rate with a resulting prolongation of diastolic interval and, thus an improvement of diastolic filling. Between 1980 and 1997, 24 randomized controlled trials of beta-blockers in heart failure were reported. These trials included a total of 3141 patients with ischaemic or non-ischaemic causes of heart failure; more than 80% were on standard ACE-inhibitor treatment. A meta-analysis showed a 31% reduction in mortality with beta-blocker and mean annual mortality being reduced from 9.7% to 7.5%.

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ACE-inhibitors in heart failure improve symptoms, haemodynamics, ventricular remodelling and survival. The survival benefit from an overview of controlled trial data (32 trials in 7105 patients) ranges from 12% to 33% 15, and it is due primarily to a reduction in deaths from worsening heart failure, but there is no clear evidence of a reduction in sudden death. The effect of Beta-blockade seems additive to that of ACE inhibition. In both CIBIS-II (Cardiac Insufficiency Bisoprolol Study) and MERIT-HF, sudden deaths were significantly reduced. Deaths

MERIT-HF (Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure) is the largest trial, which included 3991 patients with heart failure in NYHA functional class II-IV and with left-ventricular ejection fraction of under 40%, on standard therapy. Treatment with long-acting metoprolol conferred a 34% reduction in mortality, annual mortality being reduced from 11.0% to 7.2%.

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from progressive heart failure were significantly reduced in MERIT-HF and showed a trend to reduction in CIBIS-II. In MERIT-HF, sudden death was more common with less severe heart failure. Overall, this treatment effect strongly suggest an effective anti-arrhythmic action of beta-blockade, which may itself be favourably influenced by several subsidiary mechanisms, such as alterations in cardiac electrophysiology, autonomic activity, energy balance and ventricular remodelling.

Patients with severe class IV heart failure have generally been excluded from recent trials and experience in such patients is limited. The designation of patients in recent trials as "stable class IV" implies unjustified precision. Which beta-blocker is best? The US carvedilol trial 16 suggested the possibility that carvedilol may provide greater benefit than other selective agents, perhaps because of its vasodilator and other ancillary actions. The results of CIBIS-II\textsuperscript{17} and MERIT-HF, however, now indicate that the predominant effect is most probably a class effect of beta-blockers. Thus for the present, treatment with either carvedilol, bisoprolol or metoprolol can be recommended.

Patients with clinically stable heart failure and left ventricular systolic dysfunction established on standard treatment should be considered for beta-blocker therapy. Contraindications should be carefully observed. Treatment aims should be considered realistically, the principal benefits being a reduction in hospital stay and longer survival rather than symptom relief. Carvedilol, bisoprolol or metoprolol in the formulation as used in the trials can be recommended, starting with low dose and increasing gradually over weeks or months. Treatment can, with care, be established on an outpatient basis with monitoring for predictable side effects. The benefit of beta-blocker treatment for heart failure is now certain and substantial and should be incorporated into modern practice guidelines\textsuperscript{18}. The newer generation of calcium antagonists having minimal negative inotropic effect is not indicated for treating patients with symptomatic heart failure. However, it is well known that calcium antagonists have a positive lusitropic effect, which enhances myocardial relaxation and increases filling. Thus, these drugs may be helpful to improve diastolic filling in patients with diastolic dysfunction. In presence of severe reduction of left ventricular function, or when atrial fibrillation ensues, anticoagulation is necessary to prevent thromboembolic complications. This benefit of anticoagulation is useful for both systolic and diastolic dysfunction.

When all medical therapy fails in patients with end stage heart failure, cardiac transplantation becomes an option, which is not unusual for patients with systolic dysfunction but rarely occurs in cases of diastolic dysfunction. Newer drugs on the horizon for the treatment of heart failure include the neuropeptidase inhibitors, which may be an addition to therapy. These agents, such as omapatrilat, block the RAAS system and at the same time decrease degradation of atrial natriuretic peptides. Thus, these compounds have diuretic effects in addition to the effect of blocking the RAAS system\textsuperscript{19}.

Finally, nitroglycerin or isosorbide dinitrate (ISDN), which are older drugs, deserve consideration. These substances have a relaxing effect on the myocardium and have recently been studied in patients with severe aortic stenosis. Given in small doses intracoronarily nitrates reduce diastolic pressure by as much as 50\% while peak systolic pressure decreases only slightly 20. Thus, the hypertrophied myocardium appears to be especially susceptible to the effect of nitrates, with a relaxant effect demonstrated on the passive elastic properties of the heart.

**Prognosis and outcome**

Other major considerations in the treatment of heart failure include prognosis and outcome. While haemodynamics and neurohormonal factors play key roles in determining prognosis, genetic phenotype has been found to be particularly important in determining outcome. In the future it may be possible to identify patients who are at risk for premature
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dead because of their specific phenotype. An example of this concept is beta- receptor polymorphism, in which the difference of one amino acid in the beta-adrenoceptor has been found to correlate with a favourable or unfavourable prognosis over a three year period. Thus, detection of genetic polymorphism will be an important tool in the future to identify patients who are at high risk for a premature death from heart failure.

Genetic phenotype may also prove to be important in determining therapy. For example, in a recent study, AT1 receptor genotype was determined in a group of patients who received either ACE inhibitor therapy or calcium antagonist therapy. While ACE inhibitor therapy decreased cardiac wall thickness in patients with phenotypes AA, AC and CC, calcium antagonist therapy reduced myocardial mass only in patients with AA phenotype. Thus, it may become necessary to identify the genetic phenotype of a patient before an appropriate antihypertensive or heart failure drug can be initiated. Such management would be expected to help reduce costs as well as to increase the efficacy of drug therapy.


Conclusion
Morbidity and mortality can be reduced considerably in NYHA Class III and Class IV heart failure patients by the combine use of ACE inhibitors and beta-blockers. Now aldosterone antagonists have emerged as important drugs for further improving survival and quality of life in heart failure patients. Mortality rates of 10-15% per annum have become realistic in patients with advanced heart failure, and are approaching the mortality rates observed in transplanted patients.

References

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