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Current treatment of heart failure

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ABSTRACT European and American guidelines were published in 2005 that comprehensively summarised the evidence supporting currently recommended diagnostic and therapeutic approaches in HF. The need for these updates reflects the continuing progress in the management of this condition. In this article we briefly overview the current evidence-based treatment of HF. We focus on patients with reduced left ventricular systolic function, as there is no firmly evidence-based treatment for HF with preserved systolic function. Our review discusses treatments shown to favourably modify the natural history of HF when added to diuretic treatment. Diuretics should be used, as needed, to prevent sodium and water retention that can lead to peripheral and pulmonary oedema. Although diuretic treatment is empirical rather than evidence-based, it is widely agreed that the minimum dose needed to maintain 'dry weight' should be used.

KEYWORDS Co-morbidity, devices, drugs, dys-synchrony, left ventricle, transplantation

LIST OF ABBREVIATIONS African American Heart Failure Trial (A-HeFT), angiotensin-converting enzyme (ACE), ACE inhibitor (ACE-I), angiotensin-receptor blocker (ARB), beta-blocker (BB), Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM), Cardiac Insufficiency Bisoprolol Study (CIBIS-2), Cardiac Resynchronisation Heart Failure trial (CARE-HF), cardiac resynchonisation therapy (CRT), cardiac resynchronisation therapy biventricular pacing (CRT-P), cardiovascular (CV), Carvedilol Metoprolol European Trial (COMET), Carvedilol Prospective Randomized Cumulative Survival Study (COPERNICUS), Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION), Co-operative North Scandinavian Survival Study (CONSENSUS), CRT device with defibrilator (CRT-D), Digitalis Investigator Group (DIG), electrocardiogram (ECG), heart failure (HF), hydralazine and isosorbide dinitrate (H-ISDN), implantable cardioverter defibrillator (ICD), left ventricular assist devices (LVAD), left ventricular ejection fraction (LVEF), Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF), Multicenter Automatic Defibrillator Implantation Trial (MADIT), myocardial infarction (MI), New York Heart Association (NYHA), Randomised Aldactone Evaluation Study (RALES), Studies of Left Ventricular Dysfunction (SOLVD), Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), Valsartan Heart Failure Trial (Val-HeFT), Vasodilator Heart Failure Trial (V-HeFT), ventricular assist device (VAD)

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PATIENTS WITH MILD TO MODERATE FUNCTIONAL LIMITATION

Patients in NYHA functional class II and III should be treated with an evidence-based dose of an evidence-based ACE-I (see Table 1). The key trial supporting this recommendation was the treatment arm of SOLVD, reinforced by other trials in severe HF or acute MI (see Table 2). There are few contra-indications to this treatment and most patients tolerate treatment with an ACE-I. Detailed, practical advice on how to use these drugs in HF is available (see further reading).

In patients unable to tolerate an ACE-I because of a cough, an ARB should be substituted, again aiming for an evidence-based dose of an evidence-based drug (see Table 2). This recommendation is based on the results of CHARM-Alternative and a subgroup analysis of Val-HeFT, examining the small number of patients in that study not treated with an ACE-I.

Although CHARM-Alternative included patients with other causes of ACE-I intolerance, there is no reason to believe that an ARB should cause less renal dysfunction, hyperkalaemia, or hypotension. An angiotensin-receptor blocker is probably less likely to cause angio-oedema, though this is not certain.

Once established on an ACE-I (or ARB), a BB should be added. This recommendation is based on

TABLE 1 Evidence-based pharmacological treatment of HF (adapted from McMurray JJ, Pfeffer MA. Heart failure. *Lancet* 2005; **365(9474):**1877–89).

	Starting dose (mg)	Target total daily dose (mg)[2]	Doses per day[2]	Mean total daily dose achieved in outcome studies (mg)
ACE-I				
captopril	6·25	150	3	121
enalapril	2·5	20–40	2	16·6
lisinopril	2·5–5·0	20–35	1	-a
ramipril	2·5	10	1 or 2	8·7b
trandolapril	1·0	4	1	3
BBs				
bisoprolol	1·25	10	1	6·2
carvedilol	3·125	50–100	2	37c
metoprolol CR/XL	12·5 or 25	200	1	159d
Angiotensin receptor blockers				
candesartan	4	32	1	24e
valsartan	40	320	2	254
Aldosterone blockers				
eplerenone	25	50	1	43
spironolactone	25	50	1	26
Hydralazine-isosorbide dinitrate[3]				
hydralazine	37·5	225	3	143
isosorbide dinitrate	20	120	3	60

1 Based on randomised controlled trials in patients with chronic HF or HF, left ventricular systolic dysfunction or both after MI.

2 Total daily dose taken once daily or split into two or three equal portions, e.g. target total daily dose of captopril is 150 mg, taken as 50 mg three times a day (based on SAVE study).

3 Based on A-HeFT; this combination was given four times daily in V-HeFT I.

a The ATLAS trial compared high-dose (32·5–35 mg) to low-dose (2·5–5·0 mg) lisinopril; guidelines recommend 20 mg daily as a single dose.

b Based on the AIRE study in which ramipril was prescribed twice daily (target total daily dose 10 mg).

c In the COPERNICUS study in which the target total daily dose was 50 mg.

d Metoprolol succinate. The COMET trial showed that low doses of metoprolol tartrate are inferior to carvedilol.

e In CHARM-Added.

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the findings of two key trials:bisoprolol and CIBIS-2 and the MERIT-HF, which used long-acting metoprolol succinate. Both trials showed large and early reductions in mortality (and morbidity). These two trials are supported by a pooled analysis of small short-term studies with carvedilol, a larger trial with carvedilol in patients with severe HF (COPERNICUS), and a study with nebivolol in elderly patients with HF (SENIORS). The importance of using an evidence-based drug and dose is underscored by the finding of COMET that carvedilol was superior to short-acting metoprolol tartrate (though carvedilol has not been compared to metoprolol succinate). The succinate formulation used in MERIT-HF is not available in some countries (e.g. UK). There are few contra-indications to this treatment and most patients tolerate treatment with a BB. Detailed, practical advice on how to use these drugs in HF is available (see Further Reading).

In patients who remain symptomatic on the combination of an ACE-I and BB, an ARB should be added, based on the findings of CHARM-Added and Val-HeFT (see Table 2) which showed an important incremental benefit with this extra treatment. There are few contra-indications to this treatment and most patients tolerate treatment with an ACE-I, BB, and ARB. Detailed, practical advice on how to use these drugs in HF is available and careful biochemical monitoring is essential when this combination is used (see Further Reading).

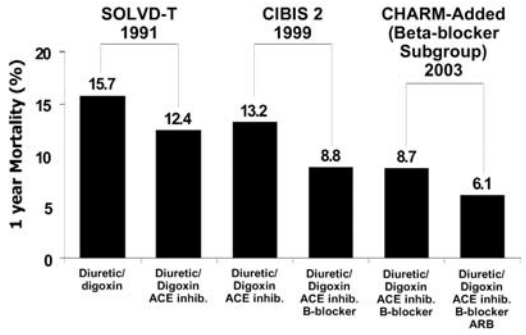

FIGURE 1 Cumulative benefit of multiple neurohumoral blockers in *mild–moderate* HF.

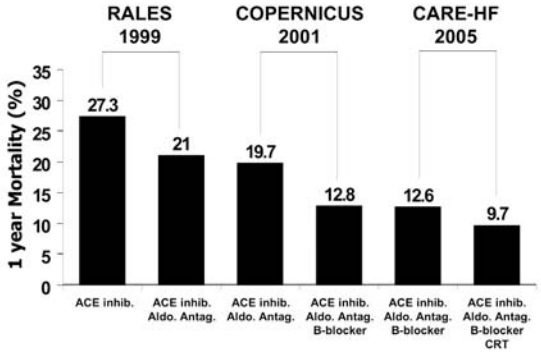

FIGURE 2 Cumulative benefit of multiple neurohumoral blockers (and CRT) in *severe* HF.

With this combination of three neurohumoral treatments, mortality and morbidity from HF has been reduced substantially (see Figure 1).

Just before the demonstration of effectiveness of ACE-I, the vasodilator combination of H-ISDN had been shown to improve survival in the placebo-controlled V-HeFT. Subsequently, in a head to head comparison between enalapril and H-ISDN (V-HeFT II), mortality was lower in the ACE-I group. Recently, in A-HeFT, when compared with placebo, H-ISDN was shown to reduce mortality and morbidity and improve symptoms in African-Americans when added to background treatment, including an ACE-I, beta blocker, and aldosterone antagonist. The place of H-ISDN in the management of other patients is uncertain but this combination should be considered in patients unable to take an ACE-I or ARB because of renal intolerance.

There is now also strong evidence that implantation of a cardioverter defibrillator in patients with a persistently low LVEF (≤ 0·35) will substantially reduce the risk of sudden death (the major risk faced by patients with milder symptoms). This treatment is recommended on the basis of two trials in HF, the SCD-HeFT and COMPANION, and one in survivors of MI, the MADIT.

PATIENTS WITH SEVERE HEART FAILURE

Both an ACE-I, based on CONSENSUS, and a BB, based on COPERNICUS, are indicated, as in patients with milder HF.

The Randomised Aldactone Evaluation Study (RALES) also showed that low dose spironolactone further reduces mortality (and morbidity) in those patients with a very poor prognosis. The main contra-indications to this treatment are hyperkalaemia and renal dysfunction. Detailed, practical advice on how to use this drug in HF is available, and careful biochemical monitoring is essential (see Further Reading). Use of spironolactone outside the trial setting in inappropriate patients, at excessive doses, and without careful monitoring has led to significant problems with hyperkalaemia and renal dysfunction.

With this combination of neurohumoral treatments, morbidity and mortality has been substantially reduced (see Figure 2).

In patients who continue to be symptomatic, the guidelines still give some support to the use of digoxin, even if in sinus rhythm, based on a subgroup analysis of the DIG trial and a meta-analysis of other trials suggesting some symptomatic benefit and a modest reduction in the risk of hospital admission with worsening HF. A major breakthrough for a subset of these severely ill patients is the use of multisite pacing to correct cardiac dys-synchrony. Patients with a prolonged QRS duration on their ECG (≥ 120 ms) are likely to have dys-synchrony. Two large trials, COMPANION and CARE-HF, showed large reductions in morbidity and mortality with these devices. It is unclear whether just a CRT device should be implanted or a device that provides CRT and also acts as a defibrillator. Cardiac transplantation may be considered in a minority of carefully selected patients with refractory HF. Left ventricular assist devices and other innovative surgical devices and approaches are still under evaluation.

TREATMENT OF CO-MORBIDITY

Co-morbidity can arise as the result of the underlying cause of HF (e.g. smoking-related lung disease, angina), HF itself (e.g. atrial fibrillation), aging (e.g. osteoarthritis), or treatments the patient is taking (e.g. gout from diuretics). Co-morbidity is important because:

a) It has a powerful influence on prognosis (e.g. diabetes, renal impairment);
b) It may modify the treatment of HF (e.g. renal dysfunction preventing use of an ACE-I);
c) The presence of HF may alter the treatment of the co-morbidity (e.g. use of a glitazones to treat

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TABLE 2 Controlled trials* in symptomatic HF with reduced systolic function (adapted from McMurray JJ, Pfeffer MA. Heart failure. *Lancet* 2005; **365(9474):**1877–89).

Trial, treatment & year published	(*n*=)	Severity of HF	Estimated first year placebo/ control group mortality	Background treatment**	Treatment added	Trial duration (years)	Primary end-point	Relative risk reduction (%)***	Events prevented per 1,000 patients treated††		
									Death	HF hosp.	Death or HF hosp.
ACE-I											
CONSENSUS 1987	253	Endstage	52	spironolactone	Enalapril 20 mg twice daily	0·54†	Death	40	146	–	–
SOLVD-T 1991	2,569	Mild – severe	15·7	–	Enalapril 20 mg twice daily	3·5	Death	16	45	96	108
BB											
CIBIS–2 1999	2,647	Moderate – severe	13·2	ACE-I	Bisoprolol 10 mg once daily	1·3†	Death	34	55	56	–
MERIT-HF 1999	3,991	Mild – severe	11·0	ACE-I	Metoprolol CR/XL 200 mg once daily	1·0†	Death	34	36	46	63
COPERNICUS 2001	2,289	Severe	19·7	ACE-I	Carvedilol 25 mg twice daily	0·87†	Death	35	55	65	81
ARBs											
Val-HeFT 2001	5,010	Mild – severe	~8·0	ACE-I	Valsartan 160 mg twice daily	1·9	Death or morbidity	13	0	35	33†††
CHARM-Alternative 2003	2,028	Mild – severe	12·6	BB	Candesartan 32 mg once daily	2·8	CV death or HF hosp.	23	30	78	60
CHARM-Added 2003	2,548	Mild – severe	10·6	ACE-I+BB	Candesartan 32 mg once daily	3·4	CV death or HF hosp.	15	28	47	39
Aldosterone blockade											
RALES 1999	1,663	Severe	~25	ACE-I	Spirolactone 25–50 mg once daily	2·0†	Death	30	113	95	–
H-ISDN											
V-HeFT-I 1986	459	Mild – severe	26·4	–	Hydralazine 75 mg three times daily – four times daily ISDN 40 mg four times daily	2·3	Death	34	52	0	–
A-HeFT 2004	1,050	Moderate – severe	~9·0	ACE-I-BB+ spironolactone	Hydralazine 75 mg three times daily ISDN 40 mg three times daily	0·83†	Composite	–	40	80	–
Digitalis glycosides											
DIG 1997	6,800	Mild – severe	~11·0	ACE-I	Digoxin	3·1	Death	0	0	79	73
CRT-P											
COMPANION 2004	925	Moderate – severe	19·0	ACE-I+BB + spironolactone	CRT	1·35†	Death or any hosp.	19	38	–	87
CARE-HF 2005	813	Moderate – severe	12·6	ACE-I+BB+ spironolactone	CRT	2·45	Death or CV hosp.	37	97	151	184
CRT-D											
COMPANION 2004	903	Moderate – severe	19·0	ACE-I+BB+ spironolactone	CRT-ICD	1·35†	Death or any hosp.	20	74	–	114

TABLE 2 Continued.

Trial, treatment & year published	(n=)	Severity of HF	Estimated first year placebo/ control group mortality	Background treatment**	Treatment added	Trial duration (years)	Primary end-point	Relative risk reduction (%)***	Events prevented per 1000 patients treated††
									Death HF hosp. Death or HF hosp.
ICD									
SCD-HeFT 2005	1,676	Mild – severe	~7·0	ACE-I+BB	ICD	3·8	Death	23	– – –
VAD									
REMATCH 2001	129	End-stage	75	ACE-I+ spironolactone	LVAD	1·8	Death	48	282 – –

* excluding active-controlled trials; ** in > 1/3 of patients: ACE-I + BB means ACE-I used in almost all patients and BB in the majority. Most patients also taking diuretics and many digoxin (except in DIG). Spironolactone was used at baseline in 5% Val-HeFT, 8% MERIT-HF, 17% CHARM-Added, 19% SCD-HeFT, 20% COPERNICUS and 24% in CHARM-Alternative; *** relative risk reduction in primary end-point. HF hosp. = patients with at least one hospital admission for worsening HF; some patients had multiple admissions.

† Stopped early for benefit; †† Individual trials may not have been designed or powered to evaluate effect of treatment on these outcomes; ††† Primary end-point which also included treatment of HF with intravenous drugs for four hours or more without admission and resuscitated cardiac arrest (both added small numbers).

diabetes; preference of colchicine over a non-steroidal anti-inflammatory drug for gout); and

d) May itself be a therapeutic target, either for prevention or treatment (e.g. ARBs to prevent diabetes and atrial fibrillation; anaemia).

A particularly important co-morbidity is atrial fibrillation, where both digoxin and warfarin are valuable.

OTHER TREATMENT CONSIDERATIONS

Organised, multi-disciplinary teams have been shown to improve prognosis and the complex, polypharmaceutical treatment of HF, which necessitates close biochemical and other monitoring, should usually be carried out within such a framework. There is growing awareness of the need for palliative and end-of-life care for patients with end-stage HF.

SUMMARY AND CONCLUSIONS

Patients with HF now have a variety of proven therapeutic options which will improve both their quality and quantity of life. Although well tolerated, these treatments require careful monitoring and patients with HF require the structured and organised multidisciplinary attention that their serious condition merits. Many new treatments are in the pipeline and more progress can be anticipated.

KEYPOINTS

- It is possible to greatly improve symptoms and survival (and reduce admissions) in patients with HF and reduced left ventricular systolic function.
- The cornerstone of treatment of HF is the combination of an ACE-I and BB, both of which should be used in every patient unless there is a clear contraindication or proven intolerance.
- For patients who continue to have symptoms, either an ARB or aldosterone antagonist should be added to improve well-being, further reduce the risk of admission, and increase survival.
- The management of patients with HF, including the initiation, up-titration, and monitoring of these treatments, is best undertaken by a multidisciplinary team that includes specialist nurses.
- Cardiac resynchronisation therapy should be considered in patients with moderate to severe persisting symptoms and a broad QRS on their 12-lead ECG, as it has been shown to improve symptoms, reduce admission, and increase survival. Advice should be sought from the National Advanced Heart Failure Service on other patients, as transplantation and additional devices may be indicated in selected cases.

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FURTHER READING

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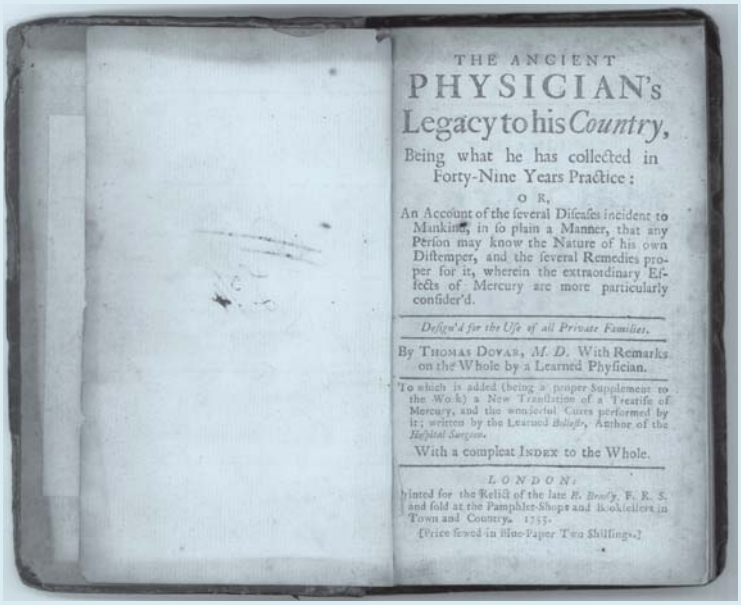

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THE QUICKSILVER DOCTOR

Thomas Dover graduated at Oxford in 1687, and for a time practised medicine in Bristol. In 1708, he was persuaded by a local sea captain, Woodes Rogers, to join a privateering expedition to raid Spanish settlements in South America. Two ships were equipped for the enterprise. Dover was appointed Captain of Marines and second in command of the Duke, a 30-gun 'man of war' with a crew of 180. On the outward journey he was in charge of the landing party which rescued the Scot Alexander Selkirk from his four-year ordeal marooned on the island of Juan Fernandez. Selkirk later became the inspiration for Daniel Defoe's *Robinson Crusoe*.

The buccaneers' round-the-world voyage lasted over three years, during which time they sacked a town in Peru, and captured a Spanish treasure ship. Dover was made Captain of the Spanish prize for the return to England, but it was a decision made with some reservation. 'His temper is so violent', wrote Captain Rogers, 'that capable men cannot well act under him'.

Satisfied with his plunder, the pirate physician returned to medical practice. Dover made his name in the medical world for two reasons, both of which can be found in his work *The ancient physician's legacy to his country*. His formula for a 'diaphoretic powder' became the most widely used opium preparation of the nineteenth century. Although popularly known as 'Dover's powder', it was listed in many pharmacopeias as 'Compound powder of ipecacuanha'. A larger part of his treatise, however, is devoted to 'the wonderful cures' which can be performed by mercury. Dover recommended its use in treating a wide variety of diseases. He was so keen on this 'miracle of nature' that his critics gave him an epithet he accepted with enthusiasm – 'the quicksilver doctor'.

John Dallas

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