Guidelines

The treatment of heart failure

The Task Force of the Working Group on Heart Failure of the European Society of Cardiology

Introduction

Throughout the last decade, the therapeutic approach to heart failure has undergone considerable change. Current treatment is directed not just towards the relief of symptoms. Additional objectives are prevention of the occurrence and progression of heart failure, modulation of the metamorphosis of asymptomatic left ventricular dysfunction to symptomatic heart failure and a reduction of mortality. There is a greater focus on preventing the onset or delaying the progression of heart failure.

Heart failure concerns not only the heart, but also the response of the body to the diminished function of the heart. Key responses include constriction of the peripheral circulation, neuroendocrine activation, cytokine activation, structural and functional abnormalities of skeletal muscle, lung function changes and retention of sodium and water. Neuroendocrine and cytokine activation are linked to the occurrence of heart failure, its clinical expression and ultimate prognosis. Consequently, the emphasis of treatment is no longer aimed solely at increasing cardiac performance or promoting the excretion of salt and water. Additional objectives are limitation of neuroendocrine and cytokine activation and the reversal of the extracardiac abnormalities.

Current medical therapy usually leads to complete or partial reduction of symptoms. In addition, life may be prolonged. In some patients elimination of the cause may normalize cardiac dysfunction. A minority of patients are treated by cardiac transplantation.

The therapeutic approaches to heart failure are multiple and include general measures, pharmacological therapy, the use of mechanical devices and surgical interventions. These approaches are not always applicable in every patient. Adverse effects and interaction between the different forms of treatment may preclude their use in some patients. Rapid deterioration, be it episodic or progressive, in the clinical condition of the

patient can require modification of the therapeutic approach under frequent and intense supervision. Novel developments are likely to result in further improvements in heart failure therapy. There is no uniform approach to the management of heart failure; treatment must be tailored to the needs of each patient.

There are wide regional differences in the approach to treatment of heart failure in Europe. These differences are attributable to variations in aetiology, health resources and historical attitudes to the use of certain drugs. Some aspects of treatment are controversial and under active investigation.

Guidelines for the Diagnosis of Heart Failure were prepared and published by the Task Force on Heart Failure of the European Society of Cardiology[1]. Subsequently, the Working Group on Heart Failure of the European Society of Cardiology was established. The present Guidelines for the Treatment of Heart Failure were prepared by a Task Force of the Working Group on Heart Failure. These guidelines are intended for use by physicians concerned with the management of heart failure. The recommendations in these guidelines should always be considered in the light of local regulatory requirements for the administration of any chosen drug or device.

Methodology for the preparation of the Guidelines on Heart Failure Treatment

This report was prepared by a Task Force from the Working Group on Heart Failure of the European Society of Cardiology (for composition, see Appendix) and written by W. J. Remme. It reflects our knowledge of heart failure treatment up to mid 1996. The advice of additional experts was sought whenever the group felt that their specific knowledge was not sufficiently represented in the core group. The document was re-drafted in the light of comments received from members of the Working Group on Heart Failure and from the Chairpersons of other Working Groups with interests in the field of heart failure (see Appendix).

The final document was approved by all members of the Task Force and subsequently submitted to the Committee for Scientific and Clinical Initiatives.

Diagnosis of heart failure — the link to management

The proper diagnosis of heart failure has several prerequisites. These are the correct recognition of the presence of heart failure, the assessment of the physiological abnormalities, the underlying aetiology, the detection of concomitant diseases which may interfere with its management, and the estimation of the severity. The European Guidelines for the Diagnosis of Heart Failure[1] concluded with a management outline (Table 1).

Aims of treatment in heart failure

The aims of heart failure management are those of the treatment of any disease in general and consist of several components (Table 2).

Prevention of heart failure

The prevention of heart failure must always be a prime objective. Many potential causes of myocardial damage can be treated and the extent of myocardial damage reduced. Examples include treatment of acute myocardial infarction, hypertension, some causes of specific heart muscle disease, prevention of re-infarction, modulation of risk factors for coronary heart disease and timely valve replacement.

When myocardial dysfunction is already present, the first objective is to remove the underlying cause of ventricular dysfunction if possible (e.g. ischaemia, toxic substances, alcohol, drugs, thyroid disease). The second objective of modern therapy is to modulate progression from asymptomatic left ventricular dysfunction to heart failure.

Primary prevention of cardiac dysfunction and heart failure is a large topic, which falls outside the scope of the current Guidelines for the Treatment of Heart Failure.

How to modulate progression from asymptomatic left ventricular dysfunction to heart failure is described on page 745 under Treatment of Asymptomatic Left Ventricular Dysfunction.

Management of chronic heart failure

In chronic heart failure, due to systolic cardiac dysfunction, the therapeutic approach consists of general measures, pharmacological therapy, mechanical devices and surgery. The currently available types of management are outlined in Tables 3 and 4.

The approach to the treatment of specific patient subgroups, i.e. the elderly, or heart failure due to predominant diastolic dysfunction, is addressed in special sections of these guidelines. The treatment of acute heart

Table 1   Management outline

1. Establish that the patient has heart failure (in accordance with the definition presented in the Guidelines for the Diagnosis of Heart Failure)
2. Ascertain presenting features: pulmonary oedema, exertional breathlessness/fatigue, peripheral oedema
3. Determine aetiology of heart failure
4. Identify concomitant disease relevant to heart failure and its management
5. Assess severity of symptoms
6. Estimate prognosis
7. Anticipate complications
8. Counsel patient and relatives
9. Choose appropriate management
10. Monitor progress and manage accordingly

Table 2   Aims of treatment

1. Prevention
(a) Prevention of disease leading to cardiac dysfunction and heart failure
(b) Prevention of progression to heart failure once cardiac dysfunction is established
2. Morbidity
Maintenance or improvement in quality of life
3. Mortality
Increased duration of life

Table 3   Treatment options — general advice and general measures

I. General advice
(a) Counselling: symptoms, monitoring of body weight
(b) Social activity and employment
(c) Travel
(d) Vaccination
(e) Contraception and hormone replacement therapy
II. General measures
(a) Diet (obesity, salt, fluid intake)
(b) Smoking
(c) Alcohol
(d) Exercise (including training programmes)
(e) Rest (only in acute heart failure or exacerbations of chronic heart failure)

failure, pulmonary oedema and cardiogenic shock is a large topic, which will be presented in a future document.

General advice

COUNSELLING

The symptoms and signs of heart failure and the prevailing treatment should be explained to patients and relatives. Emphasis should be placed on body weight. Regular measurement of body weight under standard conditions is essential. Sudden weight increases, i.e. >2 kg in 1–3 days should alert the patient to seek advice.

SOCIAL ACTIVITY AND EMPLOYMENT

Care should be taken to avoid social and mental isolation of the patient. Social activities should be encouraged. If possible, the patients should continue

Table 4   Treatment options — pharmacological therapy, devices and surgery

III. Pharmacological therapy
(a) Diuretics
(b) Angiotensin-converting enzyme (ACE) inhibitors
(c) Cardiac glycosides
(d) Vasodilator agents
(e) β-adrenoceptor antagonists
(f) Dopaminergic agents
(g) Positive inotropic agents
(h) Anticoagulation
(i) Antiarrhythmic agents
(j) Oxygen
IV. Devices and surgery
(a) Revascularization (catheter interventions and surgery), other forms of surgery
(b) Pacemakers/implantable cardioverter defibrillators (ICDs)
(c) Ultrafiltrations, haemodialysis
(d) Heart transplantation

their daily work, adapted to their physical capacity where necessary.

TRAVEL

Advice is required when air travel, high altitude, high temperatures and humidity are anticipated. In general, shorter periods of air travelling may be preferential to other forms of transport and are advisable to all patients with heart failure. Long flights may cause problems, such as dehydration, excessive leg oedema and risk of venous thrombosis in severe heart failure (NYHA class III and IV), and should be discouraged. When in the latter air travel is necessary, appropriate individual advice on fluid intake, use of diuretics and mobility during travel is required. All patients with heart failure should be advised of the effect of diet changes when travelling, the potential implications of gastrointestinal upset, and the effect of high temperature and humidity on fluid balance and use of diuretics.

VACCINATION

All heart failure sufferers should be advised to be vaccinated against influenza and pneumococcal disease, but particularly those with advanced heart failure, irrespective of aetiology, although no clinical trial data are available to delineate the real benefits of vaccination in heart failure.

CONTRACEPTION

In patients with advanced heart failure NYHA class III–IV, the risk of maternal mortality and morbidity is high. A successful pregnancy is unlikely. In these patients, pregnancy should be avoided. Counselling is required even in mild heart failure. The potential adverse effects of pregnancy on the prognosis of the mother with heart failure should always be explained.

Current methods of hormonal contraception are safer than in the past and can be advised. Low-dose oestrogen and third generation progestogen derivatives are associated with a low risk of thrombogenesis and

systemic hypertension. Intra-uterine devices remain a suitable form of contraception, except in heart failure related to valvular disease, where infections or anti-coagulating therapy may pose problems.

Observational data strongly support the idea that hormone replacement therapy (HRT) reduces the incidence of coronary events in postmenopausal women. Although the incidence of heart failure is markedly accelerated in older women, there are insufficient data to advise routine HRT to postmenopausal women with heart failure. This matter clearly needs attention, as the potential benefit in morbidity and, possibly, mortality may be considerable.

General measures

DIET

This is aimed primarily at reducing obesity. Controlling and limiting salt intake is more appropriate in advanced than mild heart failure. Documentary evidence for these traditional measures is not available at present. Liquid intake should be reduced to 1 to $1 \cdot 5 \, l \, . \, 24 \, h^{-1}$ in patients with advanced heart failure with or without hyponatraemia, except in warm climates.

SMOKING

Smoking should be strongly discouraged in all patients.

ALCOHOL

When alcoholic cardiomyopathy is suspected, alcohol intake should be forbidden.

In all other cases, daily intake probably should not exceed $40 \, g \, . \, day^{-1}$ in men and $30 \, g \, . \, day^{-1}$ in women, although there are as yet insufficient data on the effects of alcohol in patients with heart failure to support these suggestions.

EXERCISE

Deconditioning is a possible cause of alterations in muscle metabolism, which is related to symptoms, and should be avoided. Low level endurance muscle activity, such as walking, should be encouraged, whereas strenuous isometric activities should be discouraged. Specific exercise training needs to be tailored to the appropriate level of the patient's disease and always performed under medical guidance. In patients with stable heart failure, there is evidence that appropriate physical exercise and exercise training lead to an improvement in impaired exercise capacity and quality of life of the patient although the effect on prognosis is unknown[2–4]. Specific recommendations include dynamic aerobic exercise (walking) 3 to 5 times a week for 20 to 30 min, or cycling for 20 min at 70–80% of peak heart rate 5 times a week[2,3].

REST

Rest should not be encouraged in stable chronic heart failure. In patients with acute heart failure or exacerbations of chronic heart failure rest is advisable.

Pharmacological therapy (Table 4)

DIURETICS

Loop diuretics, thiazides and metolazone (Table 5). Diuretics are essential for symptomatic treatment when fluid overload is present and manifest as lung congestion or peripheral oedema. Diuretics should be administered with angiotensin-converting enzyme (ACE) inhibitors if possible. Loop diuretics, thiazides and metolazone are all used at various stages in the treatment of heart failure. Mild heart failure can be treated with a thiazide diuretic, but as heart failure worsens a loop diuretic is usually necessary. Thiazide diuretics are less effective if the glomerular filtration rate falls below 30 ml . min^{-1}, a situation that is commonly encountered in elderly patients with heart failure. In severe heart failure, thiazides have a synergistic effect with loop diuretics

Table 5(a)   Diuretics: loop diuretics, thiazides, metolazone

Initial diuretic treatment:
- Loop diuretics or thiazides.
  Always combine with ACE inhibitor.
- If GFR ≤30 ml . min^{-1} do not use thiazides, except as therapy prescribed synergistically with loop diuretics

Insufficient response:
1. combine loop diuretics+thiazides
2. increase dose of diuretic
3. with persistent fluid retention: administer loop diuretics twice daily
4. in severe CHF add metolazone or low-dose spironolactone (25–50 mg) with frequent measurement of creatinine and electrolytes

Potassium-sparing diuretics: triamterene, amiloride, spironolactone
Use only if hypokalaemia persists after initiation of therapy with ACE inhibitors and diuretics.
Start one-week low-dose administration.

Potassium supplements are usually ineffective.

GFR=glomeruler filtration rate; CHF=chronic heart failure; ACE=angiotensin converting-enzyme.

and may be used in combination[5]. It is probable that this combination is superior in terms of efficacy or adverse effects, to increasing the dose of a loop diuretic. Metolazone is a powerful diuretic which is usually used as a drug of last resort added to loop diuretics, but is not available in all European countries.

Potassium-sparing diuretics. Most patients on diuretics for the treatment of heart failure will also be treated with an ACE inhibitor. Potassium-sparing diuretics should, in general, not be used in conjunction with ACE inhibitors, although a recent controlled study indicated that low-dose spironolactone (less than 50 mg daily) in combination with an ACE inhibitor and loop diuretic does not often cause hyperkalaemia and is safe in heart failure[6]. However, if there is persisting hypokalaemia with or without concomitant ACE inhibitor therapy, potassium-sparing diuretics, such as spironolactone, triamterene and amiloride are administered to prevent or treat diuretic-induced hypokalaemia. Oral potassium supplements are less effective in maintaining body potassium stores during diuretic treatment[7] and have no proven place in preventing potassium depletion in heart failure.

If a patient is not receiving an ACE inhibitor, then potassium-sparing diuretics can be used to prevent hypokalaemia and because of their synergistic effect with loop diuretics. The combination of diuretics, an ACE inhibitor and potassium-sparing diuretics is occasionally used to overcome persisting hypokalaemia. In severe heart failure the addition of low-dose spironolactone to ACE inhibition and diuretics may be useful in the absence of hypokalaemia[6,8].

When potassium-sparing diuretics are used in patients with heart failure, particular attention should be paid to the measurement of serum creatinine and potassium. A practical approach is to measure serum creatinine and potassium every 5–7 days during initiation of treatment until the values are stable[6]. Thereafter, measurements can be made every 3 months and eventually at 6 monthly intervals. Low-dose administration of spironolactone should always be carried out and high dosages avoided.

Table 5(b)   Diuretics (oral): dosages and side effects

	Initial daily dose (mg)		Maximum recommended daily dose (mg)		Major side effects
Loop diuretics					
Furosemide	20–40		250		hypokalaemia, hypomagnesaemia, hyponatraemia,
Bumetanide	0·5–1·0		5–10		hyperuricaemia, glucose interolance, elevated LDL
Ethacrynic acid	50		400		cholesterol (high dosages), acid-base disturbance
Thiazides					
Hydrochlorothiazide	25		50–75		
Metolazone	2·5		10		
Potassium-sparing diuretics	+ACEI	− ACEI	+ACEI	− ACEI	
Amiloride	2·5	5	20	40	hyperkalaemia, rash
Triamterene	25	50	100	200	
Spironolactone	12·5	25	50	100	gynaecomastia (spironolactone)

ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS

ACE inhibitors are indicated in all stages of symptomatic heart failure due to systolic cardiac dysfunction, irrespective of the presence or absence of signs of volume overload. All patients with heart failure treated with diuretics should be considered for treatment with ACE inhibitors. ACE inhibitors should be considered as first-line therapy in patients with a reduced left ventricular ejection fraction who present with complaints of fatigue or mild dyspnoea on exertion without signs and symptoms of volume overload.

ACE inhibitors in asymptomatic left ventricular dysfunction. Asymptomatic patients with moderate to severe LV systolic dysfunction appear to benefit from long-term ACE inhibitor therapy. In the SOLVD Prevention Study, ACE inhibition administered to patients who, for various reasons, had moderate to severe LV dysfunction (ejection fraction below 35%), but were stated to be asymptomatic, reduced the development of heart failure and related hospitalization compared to those treated with placebo[9]. There was no significant effect on mortality. The data are insufficient to determine whether all asymptomatic patients with LV dysfunction should be treated with an ACE inhibitor.

ACE inhibitors in symptomatic heart failure. ACE inhibition significantly improves symptoms in patients with moderate and severe heart failure. In addition, mortality and hospitalization are reduced in patients with moderate and severe heart failure[10–12]. The effect on survival is greater than that of the combination hydralazine and nitrates[11]. ACE inhibition markedly enhances survival in patients with signs or symptoms of heart failure during the acute phase of myocardial infarction[13]. In addition to these effects on mortality, ACE inhibitors in general improve the functional status of patients with heart failure. They increase exercise capacity and decrease the number of patients hospitalized for heart failure or other cardiovascular reasons, and reduce reinfarction and unstable angina.

Major adverse effects associated with ACE inhibitors are hypotension, syncope, renal insufficiency, hyperkalaemia and angiooedema (otolaryngeal). Although it is not always easy to distinguish cough due to ACE inhibitor therapy from cough resulting from pulmonary congestion or pulmonary conditions, dry cough appears to be a frequent side effect leading to withdrawal of the ACE inhibitor in approximately 15–20% of patients. Minor adverse effects are rash and taste disturbance.

In asymptomatic LV dysfunction, reduction in systolic and diastolic blood pressure (5 and 4 mmHg, respectively)[9,10] and increases in serum creatinine ($3.5\,\mu\text{mol}\,.\,l^{-1}$)[9] are usually small in normotensive patients. Renal insufficiency and a relatively low blood pressure (serum creatinine $\leq 3\,\text{mg}\,.\,\text{dl}^{-1}$ or $265\,\mu\text{mol}\,.\,l^{-1}$ and systolic blood pressure $\geq 90\,\text{mmHg}$) are not contraindications to ACE inhibition treatment in such patients. In the CONSENSUS trial, in more severe

Table 6   The recommended procedure for starting an ACE inhibitor

1. Avoid excessive diuresis before treatment. Stop diuretics, if being used, for 24 h.
2. It may be advisable to start treatment in the evening, when supine, to minimize the potential negative effect on blood pressure, although there are no data in heart failure to support this. When initiated in the morning, supervision for several hours with blood pressure control is advisable.
3. Start with a low dose (Table 8) and build up to maintenance dosages shown to be effective in large trials (Table 7).
4. Monitor renal function/electrolytes during drug titration every 3–5 days until stable and then at 3 months and subsequently at 6-monthly intervals. If renal function deteriorates substantially, stop treatment.
5. Avoid potassium-sparing diuretics during initiation of therapy. Add potassium-sparing diuretics only with persisting hypokalaemia or refractory natriuretic therapy.
6. Avoid non-steroidal anti-inflammatory drugs (NSAIDs).
7. Check blood pressure 1–2 weeks after each dose increment.

The following patients should be referred for specialist care:
1. Cause of heart failure unknown
2. Systolic blood pressure <100 mmHg
3. Serum creatinine >130 μmol . l^{-1}
4. Serum sodium <130 mmol . l^{-1}
5. Moderate or severe heart failure
6. Valve disease

heart failure, there was on average a 10–15% increase in serum creatinine early after onset of ACE inhibitor treatment, irrespective of baseline serum creatinine[14]. In most of these patients, creatinine levels either remained stable or decreased towards pretreatment values with ongoing treatment. It should be stressed that mortality is higher among patients with elevated creatinine levels and that these patients in particular benefit from treatment with ACE inhibitors. The risk of hypotension and renal dysfunction increases in patients with severe heart failure, those treated with high doses of diuretics, elderly patients and patients with renal dysfunction or hyponatraemia. In addition, changes in serum potassium are usually small ($0.2\,\text{mmol}\,.\,l^{-1}$)[9]. Mild hyperkalaemia is not a contraindication to use ACE inhibitors. However, serum potassium levels >5.5 mmol . l^{-1} are a contraindication. Potassium-sparing diuretics should be stopped on initiation of ACE inhibitor therapy.

Absolute contraindications for initiation of ACE inhibitor treatment are bilateral renal artery stenosis and angioedema during previous ACE inhibitor therapy. A history of ACE inhibitor-induced cough is a relative contraindication. Care should be taken to exclude pulmonary congestion as the cause of cough before an ACE inhibitor is withdrawn.

Initiating ACE inhibitor therapy (Table 6). Until further trials are completed, the dose of the chosen ACE inhibitor should be titrated up to the maximum target dose used in clinical trials. Careful attention should be given to the locally approved prescribing information when initiating therapy. Target maintenance dose ranges of ACE inhibitors to be effective in various trials are shown

Table 7 Doses of ACE inhibitors shown to be effective in large, controlled trials

	Studies of mortality		
	Drug	Target dose	Mean daily dose
Studies in CHF			
Consensus Trial Study Group (1987)[10]	Enalapril	20 mg b.i.d.	18·4 mg
Cohn et al. (V-HeFT II, 1991)[11]	Enalapril	10 mg b.i.d.	15·0 mg
The SOLVD Investigators (1991)[12]	Enalapril	10 mg b.i.d.	16·6 mg
Studies after MI with or without HF			
Pfeffer et al. (SAVE, 1992)[15]	Captopril	50 mg t.i.d.	(not available)
AIRE[13]	Ramipril	5 mg b.i.d.	(not available)
TRACE[16]	Trandolapril	4 mg daily	(not available)

Table 8 Recommended ACE inhibitor maintenance dose ranges*

Drug	Initiating dose	Maintenance dose
Benazepril	2·5 mg	5–10 mg b.i.d.
Captopril	6·25 mg t.i.d.	25–50 mg t.i.d.
Enalapril	2·5 mg daily	10 mg b.i.d.
Lisinopril	2·5 mg daily	5–20 mg daily
Quinapril	2·5–5 mg daily	5–10 mg b.i.d.
Perindopril	2 mg daily	4 mg daily
Ramipril	1·25–2·5 mg daily	2·5–5 mg b.i.d.

*Manufacturers' recommendations

in Table 7. ACE inhibitor maintenance dose ranges as recommended by the manufacturers are presented in Table 8.

Care should be taken in patients with a low systolic blood pressure. Patients with a systolic level below 100 mmHg should have therapy initiated under specialist medical care. Low blood pressures (≤90 mmHg) during ACE inhibitor treatment are acceptable if the patient is asymptomatic.

Regular monitoring of renal function is necessary: (1) before, at 3–5 days, at 3 months, and 6-monthly intervals; (2) when treatment is changed, which may affect renal function (diuretics, prostaglandins and other vasodilator agents); (3) In patients with past or present renal dysfunction or electrolyte disturbances, more frequent measurements should be made.

CARDIAC GLYCOSIDES

Digoxin and digitoxin are the most frequently used cardiac glycosides. They have identical pharmaco-dynamic effects, but different pharmacokinetic profiles. Elimination of digoxin is renal. In contrast, the elimination of digitoxin, which is metabolized in the liver, is independent of renal function, which may be useful in renal dysfunction and in elderly patients. When plasma concentrations are in the normal range, signs and symptoms of cardiac glycoside intoxication are extremely rare.

Indications for cardiac glycosides. Cardiac glycosides are specifically indicated when a fast ventricular rate in atrial fibrillation is present in any degree of symptomatic heart failure due to systolic dysfunction. In asymptomatic cardiac dysfunction and atrial fibrillation cardiac glycosides may be used for heart rate control, although whether, under these circumstances, cardiac glycosides are superior to calcium antagonists (i.e. verapamil, diltiazem) or β-blockers is uncertain. Administration of cardiac glycosides, along with diuretics and ACE inhibitors, may be of symptomatic benefit in patients with NYHA Class III and IV heart failure due to systolic dysfunction in sinus rhythm and probably should be continued when patients improve to milder forms of heart failure[17,18]. Preliminary data from the DIG trial suggest that hospitalizations for and death due to worsening of heart failure may be reduced in a wider population, including mild to moderate heart failure and sinus rhythm. In contrast, digitalis glycosides may increase death due to arrhythmias. Overall, there appears to be no effect on mortality in patients with NYHA class II–IV in sinus rhythm. Contraindications to the use of cardiac glycosides include bradycardia, second- and third-degree AV block, sick sinus syndrome, carotid sinus syndrome, Wolff-Parkinson White (WPW) syndrome, HOCM, hypokalaemia, and hypercalcaemia. The dose of cardiac glycosides needs to be titrated for each patient on ventricular response rate in atrial fibrillation. Whether, in sinus rhythm, titration based on plasma digoxin levels is useful, is as yet unknown.

> *Digoxin:* The usual daily dose of oral digoxin is 0·25–0·375 mg if serum creatinine is in the normal range (in the elderly 0·0625–0·125 mg, occasionally 0·25 mg). No loading dose is needed when treating chronic conditions. Begin treatment with 0·25 mg b.d. for 2 days. Renal function and plasma potassium should always be measured before starting treatment. In renal failure, the daily doses should be reduced accordingly. As the digoxin clearance closely approximates to the creatinine clearance, the latter should be measured or calculated by the Cochroft and Gault formula:
>
> creatinine clearance = (140 − age) × weight (kg)/72 × serum creatinine (mg . 100 ml⁻¹)

creatinine clearance $= (140 - \text{age}) \times$ weight $(kg)/72 \times$ serum creatinine $(mg \cdot 100\ ml^{-1})$

Measurement of plasma digoxin concentrations is recommended in the elderly, when poor patient compliance is suspected or in the case of overdosage, during co-medication with other drugs which affect digoxin plasma concentration, such as amiodarone, quinidine or verapamil, and with insufficient rate control in atrial fibrillation.

Digitoxin: The usual oral daily dose of digitoxin is 0·07–0·1 mg . day^{-1}. An oral loading dose of 0·3 mg . day^{-1} for 3 days may be given. In heart failure, there is no need to reduce the daily dose in the absence of significant hepatic dysfunction. There is no drug interaction with verapamil, amiodarone or quinidine.

VASODILATOR AGENTS IN CHRONIC HEART FAILURE

Vasodilator agents may be used as adjunctive therapy in the management of heart failure.

Hydralazine–isosorbide dinitrate combination. This combination is an alternative therapy when ACE inhibitors are contraindicated or cannot be tolerated. Daily doses of hydralazine, up to 300 mg, in combination with isosorbide dinitrate 160 mg in the presence of cardiac glycosides and diuretics probably have some effect in reducing mortality of patients with chronic heart failure, but not in hospitalization for heart failure[19]. At these doses the combination increased exercise performance more than with enalapril[11]. The effects of hydralazine and nitrates, alone or in combination when added to ACE inhibitors is unknown. There is no evidence of proven benefit when either nitrates or hydralazine are used alone, but nitrates are often prescribed without hydralazine. Nitrates may be used for the treatment of concomitant angina. Early development of haemodynamic tolerance (tachyphylaxis) to nitrates may occur with frequent dosing (every 4–6 h), but is less with intervals of 8 to 12 h[20] or in conjunction with ACE inhibitors. Also, haemodynamic tolerance may be less during coadministration with hydralazine[21].

CALCIUM ANTAGONISTS

Calcium antagonist are not recommended for the treatment of heart failure due to systolic dysfunction. Second generation dihydropyridine-type calcium antagonists may be considered for the treatment of concomitant arterial hypertension or angina. Some second generation calcium antagonists are still under investigation with respect to their long-term effect on mortality in chronic heart failure, in addition to baseline therapy including ACE inhibition. Preliminary data indicate either no effect[22] or a positive outcome in restricted patient populations, i.e. idiopathic dilated cardiomyopathy[23]. Although in these studies the second generation dihydropyridine agents evaluated appeared to be safe and not to increase mortality, there are as yet no reasons to recommend these agents for the treatment of heart failure due to systolic dysfunction.

β-ADRENOCEPTOR ANTAGONISTS

β_1-selective blocking agents. One recent placebo-controlled trial and several smaller controlled studies suggest a beneficial effect of selective β_1-adrenergic blockade with metoprolol on cardiovascular morbidity in patients with dilated cardiomyopathy and in selected patients with heart failure[24–26]. The CIBIS Study indicated less morbidity with bisoprolol in patients with either idiopathic dilated cardiomyopathy or ischaemia[27]. Although in the latter study survival was better than with placebo in patients with heart failure of non-ischaemic origin, further confirmation is needed concerning the effect on mortality. Underlying mechanisms to explain the favourable effects of β-blockers include reduction of (cardiac) sympathetic tone, reduction in heart rate, longer diastolic periods and possibly the upregulation of the β-adrenergic receptor system.

The effect of β-blockade in heart failure has been studied predominantly in idiopathic dilated cardiomyopathy and therefore the recommendations for the use of β-blockers in heart failure are currently limited to these patients. β-blocker therapy should only be initiated under specialist medical care. Careful titration up from a very low dose is mandatory. It is not possible to predict which patient will respond. Patients with tachycardia may have a somewhat greater chance of benefit after β-blocker treatment[28]. All β-blockers may slow the heart excessively, may induce myocardial depression and can precipitate heart failure. In addition, β-blockers may initiate or exacerbate asthma and induce peripheral vasoconstriction.

Vasodilating β-blockers. Several β-blockers with additional vasodilating properties are under investigation in both ischaemic heart failure and dilated cardiomyopathy. Recently published as well as preliminary data with carvedilol, a non-selective β-blocking and α_1-blocking agent with ancillary properties, including antioxidant effects, indicate a favourable effect on morbidity with less worsening of heart failure over time in mild, moderate and severe heart failure, compared to placebo[29–31]. In addition, a favourable effect on survival in mild and moderate heart failure of both ischaemic and non-ischaemic origin has been reported[31] (Table 9).

DOPAMINERGIC AGENTS

The only clinically available orally acting dopaminergic agonist is ibopamine, which is only available for clinical use in some countries of Europe. In mild to moderate heart failure, ibopamine proved no more effective than digoxin[32]. Recently a large mortality study was stopped prematurely because of an excess of deaths in patients with severe heart failure[33]. Presently, there are insufficient data to support the clinical usefulness of this drug.

POSITIVE INOTROPIC AGENTS

Except for cardiac glycosides all positive inotropes are reserved for parenteral administration in end-stage

Table 9   Initiating dose, target dose and titration scheme of β-blocking agents in placebo-controlled large trials

β-blocker	First dose (mg)	Titration scheme total daily dose (mg)									Target dose total daily dose (mg)
Metoprolol (MCD trial)	5	wk 1 10	wk 2 15	wk 3 30	wk 4 50	wk 5 75	wk 6 100	wk 7 150			100–150
Bisoprolol (CIBIS-II)	1·25	wk 1 1·25	wk 2 2·5	wk 3 3·75	wk 4–7 5				wk 8–11 7·5	wk 12–15 10	10
Carvedilol (U.S. trials)	3·125	wk 1 6·26	wk 2	wk 3 12·5	wk 4	wk 5 25	wk 6	wk 7 50			50

heart failure, as a bridge to transplantation or in acute exacerbations of heart failure.

β-*agonists.* Available β-agonists include dobutamine (predominant β_1-, less β_2-effects) and dopexamine (predominant β_2-, some β_1-effects). In addition, dobutamine has α-adrenergic activity, while dopexamine has some dopaminergic actions. Acute haemodynamic improvement is relatively shortlasting. After several days, tolerance may occur as a result of reduced β-receptor responsiveness. In patients with severe heart failure, intermittent dobutamine administration leads to a high mortality rate, despite initial haemodynamic improvement[34].

cAMP-phosphodiesterase inhibitors. Agents with predominant phosphodiesterase (PDE)-inhibiting properties increase contractility (cardiac cAMP) and induce vasodilatation (vascular cAMP), and hence may be considered inodilator agents. Available PDE inhibitors for parenteral use provide short-term haemodynamic improvement and have some value for the treatment of acute exacerbations of heart failure[35]. Concomitant treatment with a β-adrenergic agent may be necessary, especially if systolic hypotension is present. Up to 3 weeks continuous or intermittent infusions may be useful in patients with terminal heart failure in the interim period before cardiac transplantation[36].

ANTICOAGULATION
Aspirin. In most European countries aspirin is widely used in patients with coronary artery disease, the most common underlying cause of heart failure. There is no evidence to support an effect on mortality in heart failure patients treated with long-term aspirin. In contrast, there are concerns about a possible interaction between aspirin and ACE inhibitors[37].

Oral anticoagulants. Oral anticoagulants are reputed to reduce the risk of systemic emboli in heart failure, although this hypothesis has not been adequately tested. Recent large trials do not indicate that this is a commonly encountered problem[10,12]. Oral anticoagulants

are strongly advised in patients with heart failure and atrial fibrillation. Patients with a history of systemic or pulmonary embolism, or with an endocardial thrombus, should receive anticoagulation treatment. The evidence for long-term prophylactic oral anticoagulant therapy in patients with heart failure, with enlarged hearts and sinus rhythm, is inconclusive. Treatment may be advisable in selected patients with large hearts and a low ejection fraction and is advisable in large ventricular aneurysms.

Heparin. Subcutaneous heparin is used as a prophylaxis for deep venous thrombosis in patients with heart failure confined to bed for short periods. Oral anticoagulant derivatives are preferred for long-term management. If congestive heart failure patients are receiving aggressive diuretic therapy, or are immobilized, prophylactic heparin therapy should be considered.

ANTIARRHYTHMICS
Indications for antiarrhythmic drug therapy include atrial fibrillation (rarely flutter), non-sustained or sustained ventricular tachycardia. Class I antiarrhythmics should generally be avoided as they have proarrhythmic effects on the ventricular level and an adverse effect on haemodynamics and prognosis in heart failure. Amiodarone, a class III antiarrhythmic, is effective against most common supraventricular and ventricular arrhythmias. It may restore and maintain sinus rhythm in patients with heart failure and atrial fibrillation even in the presence of enlarged left atria, or improve the success of electrical cardioversion and is the preferred treatment in this condition[38]. Amiodarone is the only antiarrhythmic drug without clinically relevant negative inotropic effects, and in fact it even has been shown to improve left ventricular systolic function. There is as yet no firm evidence that prophylactic use in patients with non-sustained, asymptomatic ventricular arrhythmias is of clinical benefit. The risk of adverse effects, such as hyper- and hypothyroidism, hepatitis, pulmonary fibrosis and neuropathy, although shown to be relatively low in recent, large, placebo-controlled trials[39–41], must be weighed against the potential benefits of amiodarone,

but the use of lower doses (100–200 mg . day^{-1}) reduces the risk. In recently published placebo-controlled heart failure trials amiodarone was associated with improved survival in only one[40]. Presently, the routine administration of amiodarone is not recommended.

OXYGEN THERAPY

Oxygen is used for the treatment of acute heart failure, but at present has no application in chronic heart failure. A recent study showed that oxygen supplementation may lead to haemodynamic deterioration in severe heart failure[42]. In patients with cor pulmonale, long-term oxygen therapy has been shown to reduce mortality[43,44].

Devices and surgery

REVASCULARIZATION PROCEDURES

Revascularization of patients with heart failure of ischaemic origin is gaining popularity because of increasing awareness that chronic left ventricular dysfunction does not necessarily mean permanent or irreversible cell damage. Chronically hypoperfused or repetitively stunned myocytes may remain viable but be hypo- or akinetic. This type of dysfunction is called 'hibernating myocardium'[1,45].

At present, there are no controlled studies available on the effect of revascularization in heart failure patients without angina pectoris. Data regarding revascularization of patients with end-stage dilated hearts due to coronary heart disease are scarce and not controlled. When pooled together, these studies show a perioperative mortality rate of 15–20%. Controlled trials are required to evaluate the effect on survival. Demonstration of viability or contractile reserve is essential for a good outcome[46,47].

PACEMAKERS

Pacemakers may play several roles in the treatment of heart failure. A pacemaker may be needed to correct an inappropriately low heart rate, or optimize the atrioventricular (AV) interval in order to increase cardiac output. In a retrospective series, lower morbidity and prolonged survival has been reported both in patients with heart failure and chronic high degree AV-block[48], and in patients with heart failure and sick sinus syndrome[49,50]. The mode of stimulation depends on the atrial rhythm, but whenever a pacemaker implantation is contemplated, AV sequence should be maintained (if possible), as morbidity may be reduced and survival may be further prolonged with dual-chamber pacing[48–50]. At present, in patients without AV block the indications for a pacemaker remain speculative. In a recent randomized controlled trial, AV sequential pacing with short atrioventricular delay did not improve cardiac pump function or clinical status over time[51].

Although the mechanism of death in a significant number of patients with severe heart failure who die suddenly may be a bradyarrhythmia[52], no method has been validated to identify such patients. In the absence of symptomatic documented bradyarrhythmias, a prophylactic pacemaker is not warranted.

IMPLANTABLE CARDIOVERTER DEFIBRILLATORS (ICD)

In patients with documented sustained ventricular tachycardia or ventricular fibrillation, the ICD is highly effective in treating recurrences of these arrhythmias either by antitachycardia pacing or cardioversion–defibrillation, thereby reducing morbidity and the need for rehospitalization. There is some evidence that the efficacy of the ICD in terminating VT/VF may translate into improved survival[53], but no definite proof in the absence of randomized trials exists. The benefit of ICD therapy may decrease with increasing degrees of heart failure[54]. Preliminary, as yet unpublished data suggest improved survival compared to conventional antiarrhythmic therapy, including amiodarone, in patients with asymptomatic LV dysfunction or mild to moderate heart failure[55]. For patients with severe heart failure and documented sustained ventricular tachyarrhythmias, ICDs at present should be considered as a bridge to transplantation, but their effectiveness in this setting has not been proven either.

ULTRAFILTRATION

Ultrafiltration has been used for patients with pulmonary oedema and/or severe refractory congestive heart failure. Ultrafiltration can resolve pulmonary oedema and overhydration in case of refractoriness to pharmacological therapies[56]. In most patients with severe disease the relief is temporary. Ultrafiltration is an aid to gain time while waiting for cardiac transplantation.

HEART TRANSPLANTATION

Heart transplantation is now an accepted mode of treatment for endstage heart failure. Transplantation significantly increases survival, exercise capacity, return to work and quality of life compared to conventional treatment, provided proper selection criteria are applied. Recent results in patients on triple immunosuppressive therapy have shown a 5-year survival of approximately 70–80%[57] and return to full-time or part-time work, or seeking employment after 1 year in about 2/3 of the patients in the best series[58].

Patients who should be considered for heart transplantation are those with severe heart failure with no alternative form of treatment. Predictors of poor survival are taken into account. The patient must be willing and capable to undergo intensive medical treatment, and be emotionally stable so as to withstand the many uncertainties likely to occur both before and after transplantation. The contraindications for heart transplantation are shown in Table 10.

Besides shortage of donor hearts, the main problem of heart transplantation is rejection of the allograft, which is responsible for a considerable percentage of deaths in the first postoperative year. The long-term outcome is limited predominantly by the consequences of immunosuppression (infection, hypertension, renal

Table 10   Contraindications for heart transplantation

- Age >60 (some centres), but varies from centre to centre
- Present (and previous?) alcohol and/or drug abuse
- Smoking (?)
- Lack of proper cooperation
- Chronic mental disease which could not be properly controlled
- Treated cancer with remission and <5 years follow-up
- Systemic disease with multiorgan involvement
- Uncontrolled infection
- Severe renal failure (creatinine clearance <50 ml . min^{-1}) or creatinine >250 μg . l^{-1}), although some centres accept patients on haemodialysis
- Fixed high pulmonary vascular resistance (6–8 Wood units and mean transpulmonary gradient >15 mmHg and pulmonary artery systolic pressure >60 mmHg)
- Recent thromboembolic complication
- Unhealed peptic ulcer
- Evidence of significant liver impairment
- Other disease with a poor prognosis

failure, malignancy, accelerated progression of athero-sclerotic vascular disease) and by transplant coronary artery disease.

Drugs to avoid or beware

The following drugs should be used with caution when co-prescribed with any form of heart failure treatment or avoided (for examples see relevant pages):

(a) Non-steroidal anti-inflammatory drugs (NSAIDs)
(b) Class I antiarrhythmics (page 743)
(c) Calcium antagonists (verapamil, diltiazem, first generation dihydropyridine derivatives (page 742)
(d) Tricyclic antidepressants
(e) Corticosteroids
(f) Lithium

Choice and timing of pharmacological therapy

The choice of pharmacological therapy in the various stages of heart failure due to systolic dysfunction is displayed in Table 11. Before initiating therapy, the correct diagnosis needs to be established and considerations should be given to the Management Outline presented in Table 1 (page 737).

Asymptomatic systolic LV dysfunction

In general, the lower the ejection fraction, the higher the risk of developing heart failure. Treatment with an ACE inhibitor is recommended in patients with reduced systolic function as indicated by a substantial reduction in left ventricular ejection fraction (≤35%) and a large heart. Consideration should be given to early

treatment when the physician for whatever reason believes symptomatic heart failure will develop in the near future.

Symptomatic systolic LV dysfunction — heart failure NYHA Class II

WITHOUT SIGNS OF FLUID RETENTION: ACE INHIBITOR
If after 4–6 weeks the ACE inhibitor is not proving effective in terms of symptoms

1. Adjust dose
2. Consider another diagnosis
3. Add a diuretic
4. When ischaemia is suspected, consider β-blockade, nitrates or revascularization before adding a diuretic
5. Consider the potential benefit of other surgical procedures, i.e. aneurysmectomy, valve surgery, when applicable

WITH SIGNS OF FLUID RETENTION: DIURETICS IN COMBINATION WITH AN ACE INHIBITOR (Fig. 1)
Both ACE inhibitors and diuretics should be administered. When symptomatic improvement occurs, i.e. fluid retention disappears, the dose of diuretic can sometimes be reduced but the optimal dose of the ACE inhibitor should be maintained. To avoid hyperkalaemia, any potassium-sparing diuretic should be omitted from the diuretic regimen before introducing an ACE inhibitor. Potassium-sparing diuretics may be added if hypokalaemia persists. Patients in sinus rhythm receiving cardiac glycosides, who have improved from severe to mild heart failure, should continue cardiac glycoside therapy.

Worsening heart failure (Fig. 2)

The most frequent causes of worsening heart failure are shown in Table 12. If patients worsen on the combination of ACE inhibitors and diuretics, cardiac glycosides are often added. Loop diuretics can be increased in dose. Combinations of diuretics (a loop diuretic with a thiazide) are often helpful. Spironolactone or potassium-sparing diuretics may be added to potentiate diuretic response, under strict control of serum potassium levels[8]. The risk of hyperkalaemia should always be considered.

Consider heart transplantation or reconsider any benefit that might be derived from coronary revascularization procedures, aneurysmectory or valve surgery.

End-stage heart failure (patients who persist in NYHA IV despite optimal treatment and proper diagnosis)

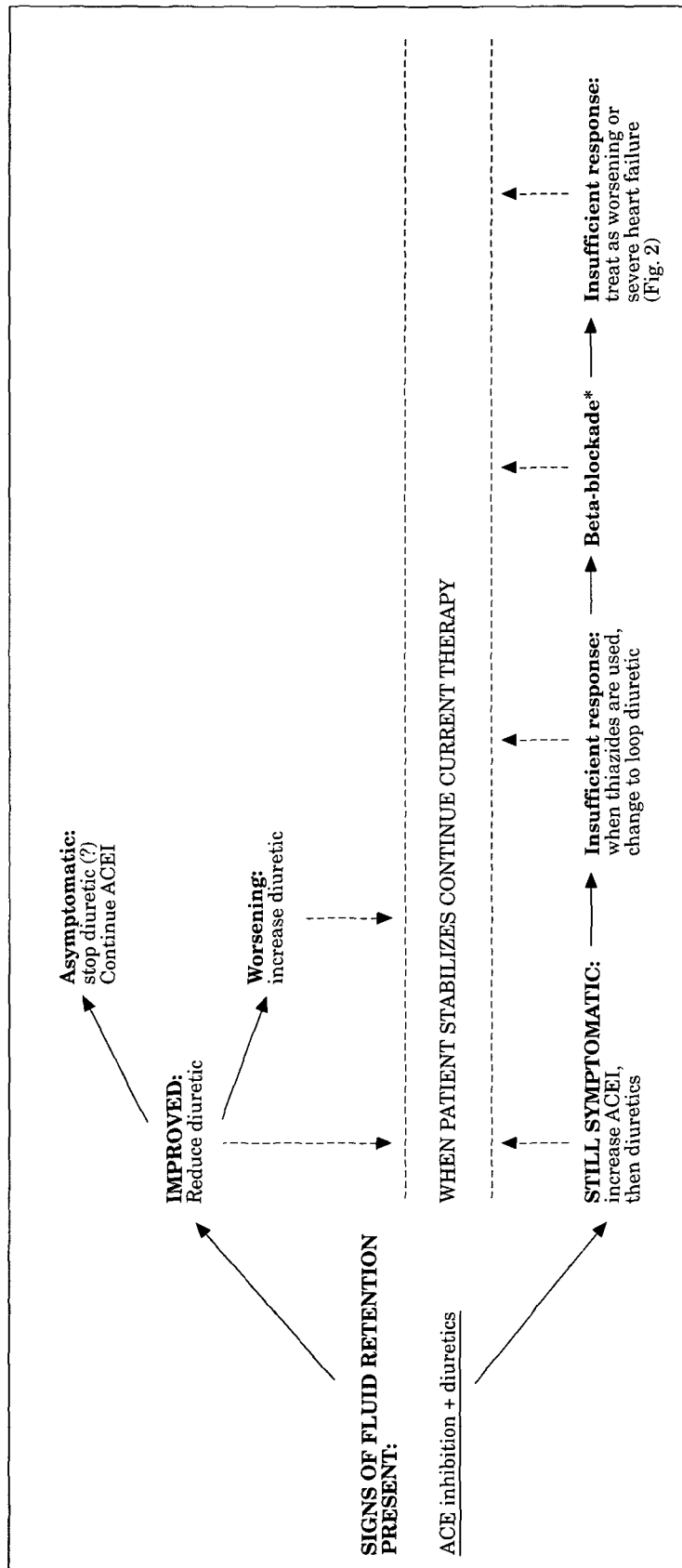Patients should be (re)considered for heart transplantation. In addition to the pharmacological treatments

SIGNS OF FLUID RETENTION PRESENT:

ACE inhibition + diuretics

IMPROVED: Reduce diuretic

Asymptomatic: stop diuretic (?) Continue ACEI

Worsening: increase diuretic

WHEN PATIENT STABILIZES CONTINUE CURRENT THERAPY

STILL SYMPTOMATIC: increase ACEI, then diuretics

Insufficient response: when thiazides are used, change to loop diuretic

Beta-blockade*

Insufficient response: treat as worsening or severe heart failure (Fig. 2)

Figure 1   Flowchart of pharmacological treatment of mild symptomatic systolic LV dysfunction NYHA II and signs of fluid retention. *Data only available for carvedilol.
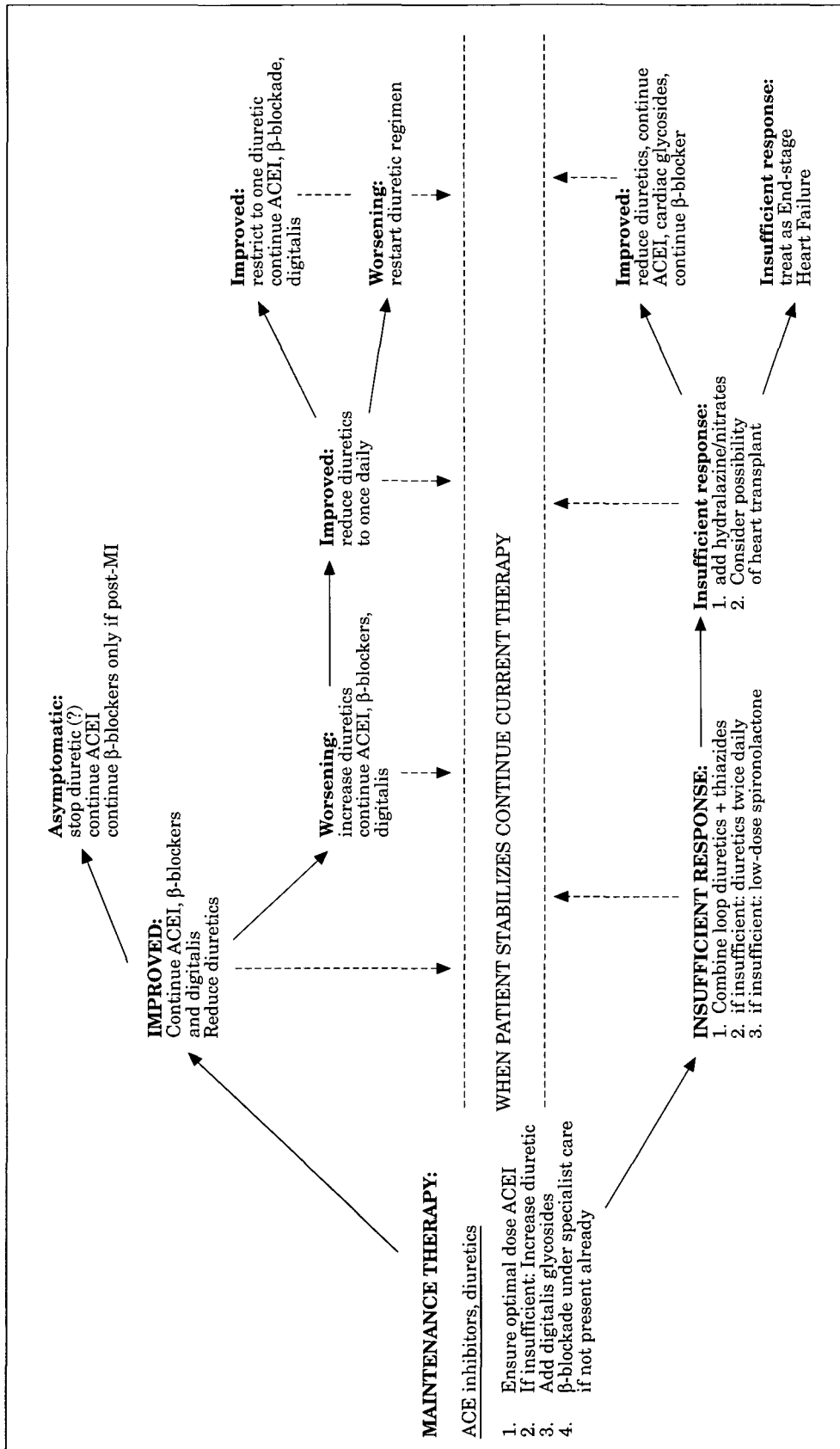
Figure 2   Flowchart of pharmacological treatment of symphomatic LV dysfunction and worsening heart failure (NYHA III–IV).

Table 11   Chronic heart failure — choice of pharmacological therapy

	ACE inhibitor	Diuretic	Potassium- sparing diuretic	Cardiacglycosides	Vasodilator (hydralazine/ISDN)	β-blocker
Systolic dysfunction						
Asymptomatic LV dysfunction	Indicated in some	Not indicated (unless ↑ BP)	Not indicated	Only with atrial fibrillation	Not indicated	Post MI
Symptomatic HF (NYHA II)	Indicated			(a) when atrial fibrillation is present, or (b) when improved from more severe HF in sinus rhythm*	If ACE inhibitors are not tolerated	Indicated (under specialist care)
− fluid retention		Indicated in some	Not indicated			
+fluid retention		Indicated	Persisting hypokalaemia			
Worsening/severe HF (NYHA III-IV)	Indicated	Indicated, combinations of diuretics	Persisting hypokalaemia; spironolactone for efficacy	Indicated	If ACE inhibitors are not tolerated or insufficient	Indicated (under specialist care)
Endstage HF (persisting NHYA IV)	Indicated	Indicated, combinations of diuretics	Persisting hypokalaemia; spironolactone for efficacy	Indicated	If ACE inhibitors are not tolerated or insufficient	Indicated (under specialist care)

BP=blood pressure; HF=heart failure; LV=left ventricular; MI=myocardial infarction.
*Preliminary data from the DIG trial suggest that digoxin may also be indicated in NYHA II heart failure and sinus rhythm.

Table 12 Most frequent causes of worsening heart failure

Non-cardiac
  Non-compliance to the prescribed regimen (salt, liquid, medication)
  Recently co-prescribed drugs (antiarrhythmics other than amiodarone, β-blockers, non-steroidal anti-inflammatory drugs, verapamil, diltiazem)
  Alcohol abuse
  Renal dysfunction (excessive use of diuretics)
  Infection
  Pulmonary embolism
  Thyroid dysfunction (e.g. amiodarone)
  Anaemia (hidden bleeding)
Cardiac
  Atrial fibrillation
  Other supraventricular or ventricular arrhythmias
  Bradycardia
  Appearance or worsening of mitral or tricuspid regurgitation
  Myocardial ischaemia (frequently symptomless), including myocardial infarction
  Excessive preload reduction (diuretics+ACE inhibitors)

outlined in the above sections, intermittent inotropic support (intravenous β-adrenergic agonists, dopaminergic agonists and/or phosphodiesterase agents) can be used in end-stage heart failure, but always should be considered as an interim approach to further treatment which will benefit the patient.

In general, it is preferred that patients on the waiting list for transplantation avoid bridging procedures; however, occasionally, circulatory support with intra-aortic balloon pumping or ventricular assist devices, haemofiltration or dialysis are necessary. These should be used only in the context of a strategic plan for the long-term management of the patient. Opiates can be used for the relief of symptoms in terminal patients.

Management of heart failure due to diastolic dysfunction

THERAPEUTIC APPROACH IN THE HEART FAILURE PATIENTS WITH PREDOMINANT DIASTOLIC DYSFUNCTION
There is very little evidence from clinical trials or observational studies as to how to treat diastolic dysfunction.

Causes of diastolic heart failure include: myocardial ischaemia, hypertension, myocardial hypertrophy and myocardial/pericardial constriction. These should be identified and treated appropriately.

1. Tachyarrhythmias should be corrected and sinus rhythm restored whenever possible.
2. Treatment can be tried with a β-blocker to lower heart rate and increase the diastolic period. Verapamil may be used for the same reason. Nitrates can be used when ischaemia is suspected. However, as with diuretics, care should be taken not to lower preload excessively.

3. Diuretics should be used cautiously so as not to lower preload excessively and thereby reduce stroke volume and cardiac output.
4. ACE inhibitors may improve ventricular relaxation directly and have a long-term effect through regression of hypertrophy.
5. Cardiac glycosides are probably contraindicated, as they may further decrease cardiac compliance.

In general, the treatment of this condition remains difficult and often unsatisfactory. One of the main problems here is that pure diastolic dysfunction may be rare, the condition often occurring in conjunction with some degree of systolic dysfunction. As conditions under which diastolic dysfunction occurs vary between patients, straight forward therapeutic algorithms are not easy to provide for the individual.

Heart failure treatment in the elderly

In the elderly, (i.e. ≥75 years of age), the therapeutic approach to systolic dysfunction is identical to that in younger heart failure patients with respect to the choice of treatment. Due to altered pharmacokinetic and pharmacodynamic properties of cardiovascular drugs in the elderly, therapy should be applied more cautiously and dosages adapted. Complicating factors include: increased myocardial stiffness, loss of myocytes; blunting of receptor function; cardiovascular function changes at rest and during exercise; renal and neuroendocrine status; sedentary lifestyle, deconditioning and a reduction in skeletal mass; changes in nutritional status habits leading to a reduced calorie/protein intake; presence of concurrent diseases and medication; non-compliance with therapy.

DIURETIC THERAPY IN THE ELDERLY
Thiazides are usually ineffective because of the reduced glomerular filtration rate resulting from increasing age and the heart failure process itself. Reduced absorption and increased excretion time of thiazides and loop diuretics can lead to delayed onset, prolonged duration and diminished action. The patient may require increased dosages, as these effects often lead to reduced diuretic effect.

Potassium-sparing diuretics, such as amiloride/triamterene, exhibit delayed elimination, and increased canrenoate potassium concentrations occur with spironolactone. Although hyponatraemia, and simultaneously hypomagnesaemia, may occur, these are usually less of a problem than hyperkalaemia. In the elderly patient, hyperkalaemia may be seen in patients treated with a combination of potassium-sparing diuretics, ACE inhibitors and NSAIDS. As the cardiac function in elderly patients is dependent on the Starling curve and baroreceptor dysregulation is common, diuretic treatment may easily result in hypovolaemic symptoms and fatigue.

ACE INHIBITORS

ACE inhibitors are effective and well tolerated in elderly patients in general. In the elderly patient, low-dose titration of ACE inhibitors is advisable. Initiation under direct supervision is recommended, while monitoring blood pressure, renal function and serum potassium levels. For logistical and budgetary reasons this is often not possible. Initiation in the outpatient clinic can be done using a slow, low-dose titration scheme.

CARDIAC GLYCOSIDES

Elderly patients may be more susceptible to the adverse effects of digoxin or digitoxin. At steady-state the digoxin mean elimination half-life increases by approximately two-fold in patients aged between 70 and 90 years. Changes in renal function which may occur with a coincidental chest infection may lead to accumulation and intoxication.

Serum digoxin/digitoxin levels should be monitored closely and kept in the low to low to normal range (between 0·7 and 1·2 ng . ml^{-1}). At this dose level, optimal haemodynamic efficacy may be obtained[59].

VASODILATOR AGENTS

Venodilating drugs, such as nitrates should be administered carefully and balanced-type (hydralazine–isosorbide dinitrate) or arterial vasodilator agents (hydralazine) may be preferable. Little data exist concerning the efficacy and safety of vasodilating agents in the elderly heart failure patient.

Arrhythmias and heart failure

Both supraventricular and ventricular arrhythmias occur frequently in heart failure. Sudden death accounts for approximately 40–50% of all deaths, decreasing in relative proportion in advancing stages of heart failure. Various mechanisms, i.e. structural cardiac changes, myocardial ischaemia and neurohormonal activation may play a role. Further precipitating factors for arrhythmias include electrolyte disturbances (hypokalaemia, hypomagnesaemia and hyperkalaemia), drug interaction with cardiac pump function or electrical stability, such as some calcium antagonists and some antiarrhythmic agents, digitalis toxicity and intercurrent diseases, e.g. hyperthyroidism and respiratory diseases.

In the approach to arrhythmias it is essential to recognize and correct these precipitating factors, improve cardiac function and diminish wall stress and reduce sympathetic activation with ACE inhibition and possibly β-blockade. Thereafter, antiarrhythmic therapy with amiodarone for severe, symptomatic non-sustained tachyarrhythmias (page 743) or in selected cases with sustained VT/VF with ICD (page 744) may be considered. Whether amiodarone improves survival in heart failure needs further confirmation.

For chronic atrial fibrillation, electrical cardioversion or anticoagulation should always be considered,

although its success rate may depend on left atrial size. Amiodarone may convert atrial fibrillation to sinus rhythm and improve the success rate of electrical cardioversion[38]. With permanent atrial fibrillation, rate control is mandatory. In asymptomatic patients, β-blockade, verapamil or digitalis glycosides may be considered, in symptomatic patients digitalis glycosides are the first choice. Combination with amiodarone may be necessary with measurement of digoxin plasma levels. Although the combination of digitalis glycosides and β-blockade may be favourable for rate control, there are few data on heart failure.

Symptomatic systolic LV dysfunction and concomitant angina or hypertension

Specific recommendations in addition to general treatment for heart failure due to systolic LV dysfunction.

If angina is present:
1. consider coronary revascularization
2. add long-acting nitrates
3. if not successful: add second generation dihydropyridine derivatives or, if not administered already, carefully a beta-blocking agent (see recommendations page 742 and 743)

If hypertension is present:
1. optimize dose ACE inhibitors and diuretics
2. add hydralazine
3. if not successful: try second generation dihydropyridine derivatives

Drugs, devices and surgical procedures under investigation — future developments

ANGIOTENSIN II (A-II) RECEPTOR ANTAGONISTS, RENIN INHIBITORS

Angiotensin II (A-II) antagonists are used for hypertension. At present, their role in the treatment of heart failure either instead of or in addition to ACE inhibitors is evaluated. They may prove to be better tolerated than ACE inhibitors. Long-term trials in heart failure are required.

ARGININE VASOPRESSIN (AVP) ANTAGONISTS

A number of AVP antagonists are undergoing early clinical evaluation in heart failure. Little data are available at present.

ENDOTHELIN ANTAGONISTS

Several selective and non-selective endothelin antagonists have shown short-term beneficial effects in

experimental heart failure. In man haemodynamic improvement occurs as well. Long-term trials are needed to evaluate the potential symptomatic benefit of these agents.

NEUTRAL ENDOPEPTIDASE INHIBITORS
The therapeutic potential of the diuretic, natriuretic and vasodilator peptides atrial and brain natriuretic factor (ANP/BNP) in heart failure has led to several approaches, including direct intravenous administration and inhibition of the enzyme responsible for its rapid breakdown, a neutral endopeptidase (NEP).

Preliminary clinical trials in patients with mild heart failure indicate that chronic oral administration of a NEP inhibitor is associated with sustained elevation of ANP levels, diuresis, natriuresis and haemodynamic improvement[60].

A comparison of the haemodynamic effects of standard diuretic therapy with an NEP inhibitor had indicated a more favourable profile for NEP inhibition, together with absence of neuroendocrine stimulation. Since antagonism of ANP by the renin-angiotensin system is present in heart failure, long-term ACE inhibition in association with an NEP inhibitor is an attractive option.

POSITIVE INOTROPIC THERAPY
Agents which increase contractile force by enhancing the sensitivity of troponin C for calcium (calcium sensitizers), are currently evaluated in patients with heart failure. Most compounds have additional effects, PDE-inhibiting properties (pimobendan[61], vesnarinone[62] or calcium channel-blocking properties (DPI 210-106[63])). Studies with previously available positive inotropic drugs acting predominantly through cAMP-dependent mechanisms have been associated with increased mortality[64-66].

METABOLIC THERAPY
Metabolic therapy could be an alternative approach in the treatment of heart failure. L-Carnitine, essential for FFA-acid transport across the inner mitochondrial membrane, is pivotal in myocardial energy production and a life-saving treatment in dilated cardiomyopathy due to a primary or secondary carnitine deficiency[67]. These cases are rare and require a precise diagnosis based on carnitine assay and myocardial biopsy. In chronic heart failure due to idiopathic or ischaemic cardiomyopathy, cardiac carnitine levels are decreased[68]. Several small studies indicate haemodynamic and functional improvement following long term L-carnitine or L-propionylcarnitine therapy[69].

Other metabolic compounds include coenzyme Q10 and taurine. Q10 has been shown to have small beneficial effects on cognitive symptoms as well as exercise duration. The clinical importance is unclear.

CARDIOMYOPLASTY FOR TREATMENT OF SEVERE CONGESTIVE HEART FAILURE
Cardiomyoplasty has only been applied in a limited number of patients (approximately 400 worldwide) and

is still undergoing investigation. Many of the early treated patients had either contraindications for heart transplantation or were in an extremely poor cardiac or general condition. In the selection of patients, class IV patients should be avoided since they have a high operative mortality. Patients must be able to survive the 3 months between isolation of the latissimus dorsi muscle and the final functioning of the muscle. Controlled studies with a long-term follow-up are needed before definite recommendations can be made.

ARTIFICIAL HEART
While undergoing continuous clinical investigation this device has been used for periods up to 1 year, largely as a bridge to cardiac transplantation.

VENTRICULAR ASSIST DEVICES
A number of ventricular assist devices are currently undergoing clinical evaluation.

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Appendix

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