Fortnightly Review

Diagnosis and management of heart failure

Henry J Dargie, J J V McMurray

Doctors diagnose heart failure when patients whom they suspect of having heart disease develop fatigue, dyspnoea, or oedema. By these standards, this is a terminal condition because in severe cases its annual mortality may exceed 60%.[1] Even in so called mild cases detected in community screening programmes such as the Framingham study the five year mortality approached 50%.[2] These survival rates are worse than for many of the common forms of cancer, emphasising that heart failure is indeed a malignant condition. Heart failure also imposes a heavy burden of symptoms. In studies of the major chronic illnesses such as diabetes, arthritis, and hypertension, heart failure had the greatest negative impact on quality of life, and not just slightly so.[3,4] The high morbidity is also reflected in the number of hospital admissions for heart failure, about 120 000 cases each year in the United Kingdom.[5,6] These represent 5% of all adult medical and geriatric admissions and are about the same as the number of admissions for acute myocardial infarction.[7]

Heart failure is a serious public health problem, with a prevalence in the United Kingdom, Scandinavia, and the United States of about 0·4-2% overall and 10% in elderly subjects.[8] There is a sharp upturn in both prevalence and incidence in older populations (fig 1). Heart failure is also expensive, costing the NHS about £360 million a year in diagnosis and management, 60% of which is spent on hospital treatment.[9] This financial burden is similar to that of stroke and asthma.

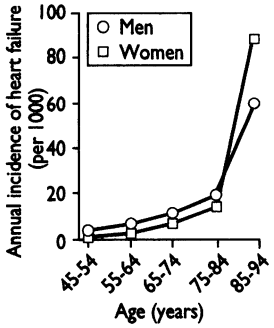

FIG 1—*Annual incidence of heart failure. From the Framingham study*[2]

Summary points

- Heart failure is a malignant condition with high rates of morbidity and mortality even in so called mild cases
- Left ventricular dysfunction is the main cause of heart failure, and echocardiography can quickly distinguish less common but reversible causes
- The most effective medical treatments for heart failure are diuretics, usually a loop diuretic, and angiotensin converting enzyme inhibitors
- If patients remain symptomatic or cannot tolerate angiotensin converting enzyme inhibitors, other treatments such as hydralazine and isosorbide dinitrate or digoxin may be used, and as a last resort cardiac transplantation may be considered
- Concomitant problems that may need treatment are atrial fibrillation, angina, and ventricular arrhythmia

Large trials of patients with different stages of heart failure

Acute myocardial infarction

Second international study of infarct survival[10]
Third international study of infarct survival[11]
Gruppo Italiano per lo Studio della Streptochinasi nell-Infarto Miocardico[12]
Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico[13,14]
Cooperative new Scandinavian enalapril survival study[15]
Survival and ventricular enlargement[16]

Asymptomatic left ventricular dysfunction

Studies of left ventricular dysfunction[17]

Congestive heart failure, symptoms on effort (New York Heart Association class II or III)

Veterans heart failure trials[18,19]
Studies of left ventricular dysfunction[20]

Congestive heart failure, symptoms on effort or at rest (New York Heart Association class III or IV)

Prospective randomised milrinone survival evaluation[21]

Congestive heart failure, symptoms at rest (New York Heart Association class IV)

Cooperative north Scandinavian enalapril survival study[1]

Recently, interest in heart failure has increased because of a series of big trials, some of which are listed in the box. Patients in three of these trials represent the late,[1] middle,[20] and early phases[18,19] of left ventricular dysfunction, and clinical expression varies from apparent normality to serious impairment of the quality of and potential length of life. Recognition of such a range of states has led to a broadening of our concept of heart failure beyond the familiar clinical symptoms of fatigue, dyspnoea, and fluid retention. With so much attention on patients with left ventricular dysfunction, it must be remembered that heart failure may also result from disease of any part of the heart, including the pericardium, valves, and endocardium. In Western countries coronary heart disease is by far the main cause of heart failure due to left ventricular dysfunction, with dilated cardiomyopathy being much less common.[8] Other causes are less common, but the poor prognosis for heart failure due to myocardial dysfunction demands that full investigation be carried out to exclude one of the less common but potentially reversible causes of heart failure.

How to recognise heart failure

Heart failure is not a diagnosis in itself. The patient usually but not always has a history of heart disease,

Department of Cardiology, Western Infirmary, Glasgow G11 6NT
Henry J Dargie, *consultant cardiologist*

Cardiac Department, Western General Hospital, Edinburgh EH4 2XU
J J V McMurray, *consultant cardiologist*

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most commonly myocardial infarction or some form of coronary heart disease. Clinical diagnosis is relatively easy in the full blown condition with symptoms of fluid retention, fatigue, and dyspnoea and sometimes also signs such as tachycardia, a third heart sound (with or without a gallop rhythm), and cardiomegaly.

A chest *x* ray picture is useful mainly for evidence of pulmonary oedema or venous hypertension. The heart is likely to be enlarged, but little other information will be forthcoming from the radiograph. Electrocardiography is helpful because the presence of pathological Q waves may indicate previous myocardial infarction, the main abnormality may be left ventricular hypertrophy, and an arrhythmia may be present. Unlike angina, the electrocardiogram in heart failure is rarely normal. If it is, then either a rare condition is present or the diagnosis itself needs to be revised. One of the rare conditions that may cause this finding is constrictive pericarditis, although even in this case some abnormality such as low voltage complexes is often present.

ECHOCARDIOGRAPHY

Echocardiography is the key investigation since reversible causes of heart failure such as valve or pericardial disease can be excluded in a few seconds. The usual finding, however, will be the presence of a dilated poorly contracting left ventricle. In cardiological practice it has been customary to record the degree of left ventricular dysfunction by calculating the left ventricular ejection fraction. This is a throwback to the days when left ventricular dysfunction could only be assessed invasively with a left ventricular angiogram, from which the left ventricular ejection fraction was calculated. Unfortunately this practice has been retained with echocardiography. It is rarely necessary to be so specific since simple inspection of the echocardiogram with measurement of the left ventricular end diastolic and systolic dimensions and calculation of the fractional shortening will suffice for most cases of heart failure.

In the case of valve disease, colour flow Doppler ultrasonography can indicate the presence and extent of valve incompetence, while continuous or valve wave Doppler ultrasonography can measure the velocity of blood flow across valves from which stenotic gradients may be calculated. Suspected heart failure should therefore prompt a doctor to request an echocardiogram rather than, as might have been the case in the past, a chest *x* ray picture.

INVASIVE INVESTIGATION

There are three reasons for invasive investigation of selected patients. Firstly, patients with coronary heart disease should be identified since some may be suitable for revascularisation. The concept of "hibernating" myocardium has been advanced to explain the reversible left ventricular dysfunction that occurs in the presence of chronic hypoperfusion as a result of coronary artery stenoses.[22] In theory this should be assessed by the response to inotropic agents such as dobutamine, in which the hibernating segment regains contractility—shown by echocardiography or radionuclide angiography. In practice the decision to recommend revascularisation is often made on prognostic grounds since coronary artery bypass grafting seems to confer the greatest survival advantage in patients with impaired left ventricular function and triple vessel disease.[23] This will be considered justified in some patients, but there is as yet no evidence that angioplasty has a prognostic role in this situation.

Electrophysiological evaluation and endomyocardial biopsy may be required in specific situations such as recurrent serious ventricular arrhythmia or in the diagnosis of specific heart muscle diseases such as amyloidosis or haemochromatosis. In routine practice these investigations are not usually considered necessary, although ambulatory monitoring may be performed more frequently in the future as more is learnt about the prognostic and therapeutic aspects of "silent" ventricular arrhythmia.[24]

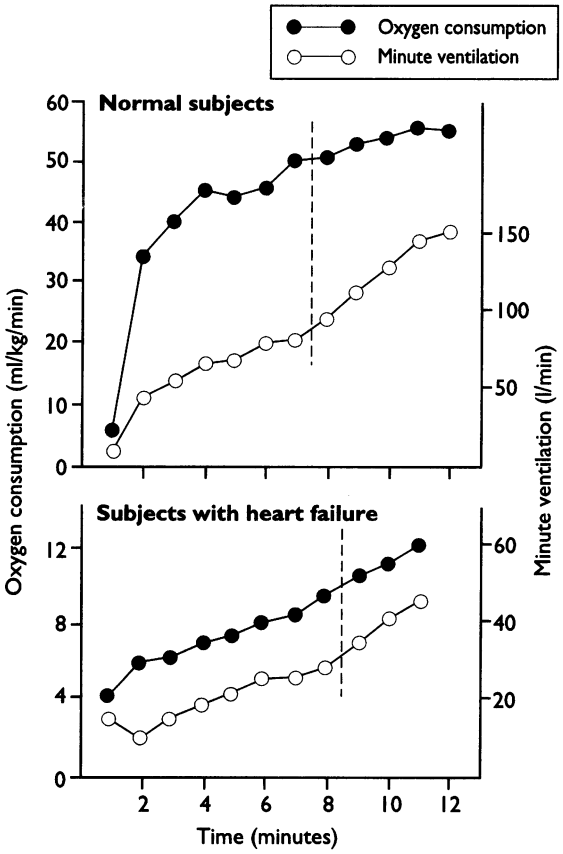

FIG 2—*Maximum oxygen consumption and volume ejection during graded exercise test by normal subjects and subjects with heart failure. Dotted line is anaerobic threshold*

EXERCISE TESTING

Peak oxygen uptake by the body during exercise defines a patient's circulatory status, and the ability to perform exercise is an indication of the ability of the heart to deliver oxygen to metabolising tissues. Thus exercise testing allows a doctor to assess in physiological terms whether heart failure exists and its severity. During a graded exercise test the oxygen consumption of a normal subject may exceed 50 ml/kg/min and will have a lower limit of 20 ml/kg/min, which is the upper level of oxygen consumption in a subject with heart failure (fig 2). Since resting oxygen consumption is 3·5 ml/kg/min (one metabolic equivalent), the normal lower limit is about six metabolic equivalents. Oxygen consumption is measured in specialised centres to assess patients' progress and to detect those who should be considered for cardiac transplantation since symptoms and effort capacity are not always closely related. Patients with a maximum oxygen consumption of less than four metabolic equivalents have an extremely poor prognosis and should be considered assuming they meet other criteria described later.

NEUROENDOCRINE ASSESSMENT

Increased concentrations of several neurohormones are typical of severe heart failure, and concentrations of noradrenaline and renin are directly related to prognosis.[8] However, these are not widely used in clinical practice, though there is considerable interest in the measurement of some cardiac natriuretic peptides as more reliable indicators of left ventricular dysfunction. Work is being carried on to assess whether these peptides can be used as a screening or

monitoring test for the presence and progression of left ventricular dysfunction.[25]

Treatment of heart failure

There are two main considerations in the treatment of patients with heart failure. Firstly, there is treatment for the failing pump itself and its major consequences, fluid retention and vasoconstriction. Equally important is the treatment of associated problems, some of which reflect the underlying cause of pump dysfunction (for example, angina pectoris) and some of which are secondary to heart failure (for example, arrhythmias). The treatment of these problems in a patient with heart failure is often different from that in a patient who does not have heart failure.

DIURETICS

There is no more effective symptomatic treatment for heart failure than diuretics.[8 26] Four main principles underlie their use in heart failure (see box), and loop diuretics are usually used. The effective daily dose of frusemide is 40 mg (equivalent to 1 mg bumetanide), but reduced diuretic efficacy may lead to 80-120 mg daily being necessary. At this stage a second diuretic—either a thiazide such as bendrofluazide (5-10 mg daily) or metolazone (2-10 mg daily)—should usually be added. Combination treatment is often required for only a few days. Careful monitoring of hydration status and blood chemistry is necessary during this time, usually requiring inpatient supervision.

TABLE I—*Effects of different treatments for heart failure. From McMurray and Dargie*[29]

Treatment	Events prevented per 1000 years of treatment or *per 1000 patients treated
Treatment of mild hypertension	1-2 strokes
Lipid lowering treatment (gemfibrozil)	2-3 cardiac events
β Blockade after myocardial infarction:	
Intravenous	6 deaths*
Oral	17 deaths
Intravenous streptokinase after myocardial infarction	25 deaths*
Enalapril:	
For severe chronic heart failure	160 deaths
For mild or moderate chronic heart failure	16 deaths and 116 admissions

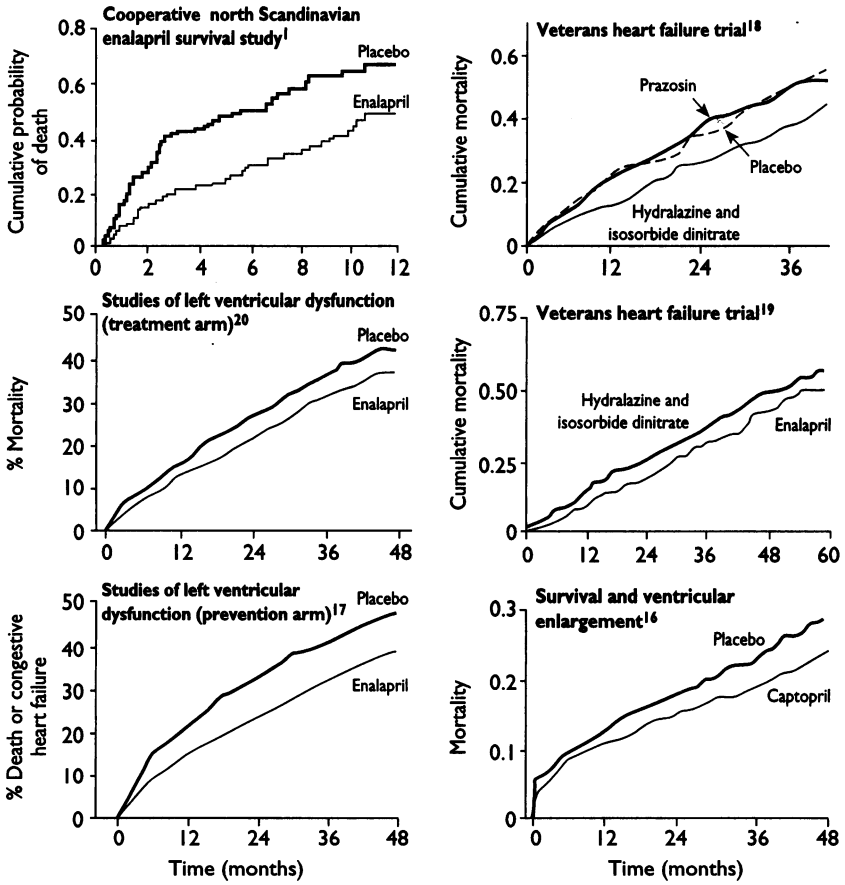

FIG 3—*Effects of angiotensin converting enzyme inhibitors on survival of patients with various grades of left ventricular dysfunction*

Principles of using diuretics for heart failure

- Use in moderation; avoid excessive doses of any single drug
- Make use of synergism between different classes of drugs, especially in cases of diuretic resistance (the principle of sequential nephron blockade)
- Monitor blood chemistry to avoid uraemia, hypokalaemia, and hyponatraemia
- Use in combination with an angiotensin converting enzyme inhibitor unless this is not tolerated

ANGIOTENSIN CONVERTING ENZYME INHIBITORS

The primary action of these drugs is to inhibit the production of the hormone angiotensin II, a powerful vasoconstrictor which has direct and indirect renal effects.[8] Secondly, they increase concentrations of the vasodilator bradykinin by inhibiting the enzyme responsible for its degradation. They also have important effects on the kidneys, electrolytes, and the electrical stability of the heart. When given with diuretics, angiotensin converting enzyme inhibitors improve the symptoms and signs of all grades of heart failure and improve exercise tolerance.[1 20 27] Progression of heart failure from mild to severe is reduced,[28] as is hospitalisation,[20 27] and survival is improved in all grades of heart failure (fig 3).[1 20 24] Indeed, inhibition of angiotensin converting enzyme represents one of the most effective treatments for heart failure available (table I).[29] All patients with heart failure should therefore be considered for such treatment even if they have been rendered asymptomatic by a diuretic.

Guidelines for use

Certain precautions should be taken before treatment is started (fig 4). Potassium supplements and potassium sparing diuretics should be stopped, while other diuretics should be stopped temporarily 24 hours before the first dose of angiotensin converting enzyme inhibitor—they can be resumed the next day. The patient should sit or lie down for two to four hours after the first dose, depending on the drug used. A low dose should be given initially—for example, captopril 6·25 mg or enalapril 2·5 mg—and regular treatment can then usually be started at an intermediate dose—captopril 12·5 mg thrice daily or enalapril 2·5 mg twice daily. The patient should be reviewed after one or two weeks to check blood chemistry and test for symptomatic hypotension, and the drug dose should be modified accordingly. Provided the patient has not experienced significant hypotensive symptoms or a significant rise in serum creatinine or potassium concentration (>200 μmol/l or 5·0 mmol/l respectively), the dose of angiotensin converting enzyme inhibitor should be increased. Larger doses such as enalapril 10 mg twice daily or captopril 25-50 mg thrice daily are recommended as they have been shown to be beneficial in clinical trials (table II). Two recent studies have also shown greater benefit with higher doses of such drugs.[34 35] For certain high risk conditions (box), patients should be admitted to hospital to start treatment.

Adverse effects of angiotensin converting enzyme inhibitors

Hypotension—Symptomatic hypotension occurred

High risk conditions warranting hospital admission for starting treatment with angiotensin converting enzyme inhibitors

- Severe heart failure (New York Heart Association class IV); patients with a dose of >80 mg frusemide or equivalent
- Low systolic blood pressure (<100 mm Hg)
- Low serum concentration of sodium (<130 mmol/l) or potassium concentration >5·5 mmol/l
- Possible hypovolaemia (low jugular vein pulse, recent diuresis or fluid loss, high diuretic dose, or combination diuretic treatment)
- Additional vasodilator treatment (excluding nitrates)
- Existing renal dysfunction (serum creatinine concentration >200 μmol/l)
- Severe diabetes mellitus with associated renal disease
- Severe generalised atherosclerosis (especially if intermittent claudication and arterial bruits are present)
- Severe chronic obstructive airways disease and pulmonary heart disease (cor pulmonale)

in only 2·2% of patients with moderate left ventricular dysfunction after treatment with enalapril.[20] If hypotension does occur the patient may be dehydrated, in which case a treatment can often be restarted after correction of dehydration; obstructive valve disease might be present; or the patient could have diastolic rather than systolic left ventricular dysfunction.

Renal dysfunction—In trials of patients with mild and moderate heart failure only small changes in serum creatinine and urea concentration (8·8 μmol/l and 1·2 mmol/l respectively) occurred after treatment.[19 20] Among patients with severe heart failure, many of whom had abnormal baseline blood chemistry, serum creatinine concentration was as likely to fall as it was to increase after starting enalapril treatment.[1] As with symptomatic hypotension, renal dysfunction is often exacerbated by dehydration. Non-steroidal anti-inflammatory drugs may also cause renal dysfunction and should be avoided if possible in patients receiving angiotensin converting enzyme inhibitors.

Hyperkalaemia—Only a small proportion of patients with mild and moderate heart failure develop hyperkalaemia, and this has rarely been a cause of study withdrawal in any of the large trials. Dehydration, non-steroidal anti-inflammatory drugs, and potassium sparing diuretics increase the risk of hyperkalaemia.

Cough—Cough is common in patients with heart failure (31% of controls and 37% of enalapril treated patients with moderate heart failure[20]). In trials, however, there were either no or very few withdrawals among patients treated with angiotensin converting enzyme inhibitors because of cough.[1 19] Cough therefore does not seem to be a major side effect of angiotensin converting enzyme inhibitors in heart failure.

TABLE II—*Doses of angiotensin converting enzyme inhibitors shown to be effective in various trials*

Study	Drug	Target dose	Mean daily dose
Studies of symptoms and exercise tolerance			
Captopril Multicenter Research Group[30]	Captopril	100 mg thrice daily	221 mg
Cleland *et al*[31]	Captopril	50 mg thrice daily	93·75 mg
Cleland *et al*[32]	Enalapril	40 mg once daily	36·5 mg
Creager *et al*[33]	Enalapril	20 mg twice daily	23·6 mg
Studies of mortality			
Cooperative north Scandinavian enalapril survival study[1]	Enalapril	10 mg twice daily	18·4 mg
Veterans heart failure trial[19]	Enalapril	10 mg twice daily	15·0 mg
Studies of left ventricular dysfunction[20]	Enalapril	10 mg twice daily	16·6 mg
Survival and ventricular enlargement[16]	Captopril	50 mg thrice daily	NA

NA=Not available.

OTHER VASODILATORS

Hydralazine and isosorbide dinitrate—This combination improves symptoms, exercise tolerance, and possibly survival in patients with congestive heart failure.[18 19] This combination is not widely used in Europe because of side effects and the superiority of angiotensin converting enzyme inhibitors, which give a higher survival benefit (fig 3).[19] It would be of interest to know whether the combination is of benefit when given in addition to an angiotensin converting enzyme inhibitor.

Flosequinan—This is a new arterial and venous vasodilator that appears to inhibit vasoconstriction by blocking a second messenger pathway in the vascular smooth muscle cell.[36] A dose of 100 mg given in addition to diuretics is of symptomatic benefit in heart failure.[36 37] However, it has also been shown that a daily dose of 100 mg flosequinan increased mortality in patients with heart failure,[38] and, since the rate of hospitalisation was greater with the 75 mg dose than placebo, Boots Pharmaceuticals have withdrawn flosequinan from the market (letter to doctors from Boots Pharmaceuticals, 17 July 1993).

DIGOXIN

There has been recent re-evaluation of the role of digoxin in heart failure.[39-41] Though usually thought of as an inotrope, digoxin is now known to have other possibly more important effects in heart failure. These are neuroendocrine suppression, especially

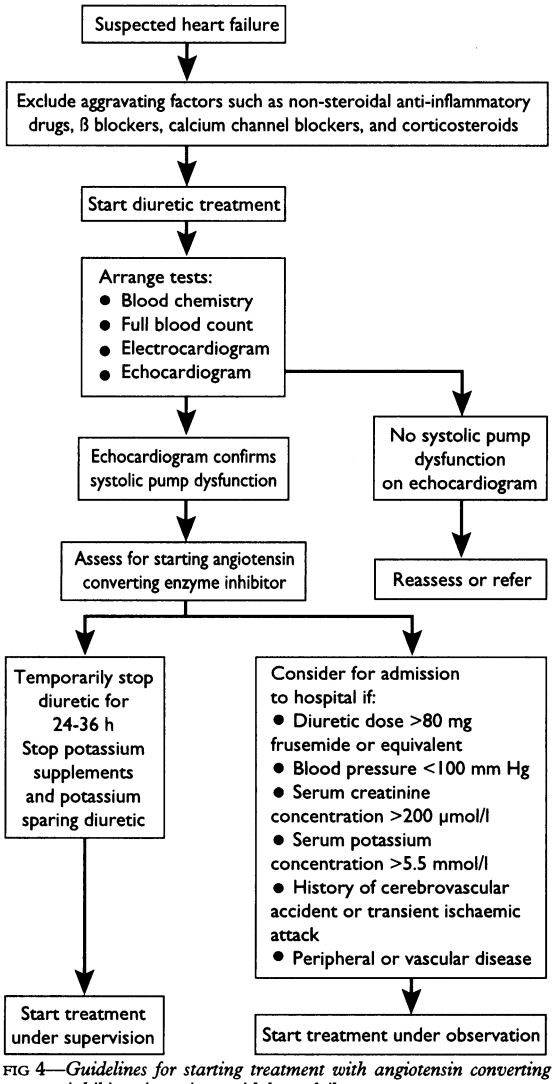

FIG 4—*Guidelines for starting treatment with angiotensin converting enzyme inhibitors in patients with heart failure*

sympathetic nervous system inhibition, and arterial vasodilatation, probably mainly indirectly. Digoxin, of course, has complex direct and indirect electrophysiological effects.

Four large, double blind, randomised, placebo controlled trials and several smaller studies have shown digoxin to be of benefit in patients with heart failure in sinus rhythm.[39] The size of this benefit is, however, probably smaller than that achieved with angiotensin converting enzyme inhibitors, which are to be preferred for their effect on prognosis. Digoxin, however, has been convincingly shown to be of benefit when given as well as an angiotensin converting enzyme inhibitor and diuretic (fig 5).[42] The indications for digoxin are therefore as an adjunct to diuretics and angiotensin converting enzyme inhibitors in patients who remain symptomatic and as an adjunct to diuretics in symptomatic patients who cannot tolerate an angiotensin converting enzyme inhibitor. Digoxin is, of course, indicated separately for the treatment of concomitant atrial fibrillation. Most trials showing clinical benefit have aimed to achieve plasma digoxin concentrations at the upper end of the therapeutic range (0·72-2·5 mg/ml),[41] but lower concentrations may also be of benefit, though this possibility requires further investigation.[42]

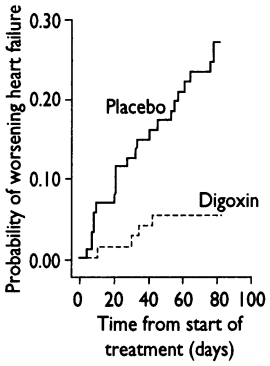

FIG 5—*Probability of heart failure worsening among patients treated with angiotensin converting enzyme inhibitor who also received either digoxin or placebo. From Packer et al*[42]

The incidence of digoxin toxicity in outpatients appears to be low, about one episode for every 20 years of treatment. This is supported by the recent large digoxin trials where the incidence of adverse effects with digoxin has been no different than with placebo.[39] Some potential drug interactions are relevant to heart failure. Hypokalaemia (caused by diuretics) increases the risk of digoxin toxicity. A quinidine-like interaction is believed to occur with quinine, a drug frequently given for leg cramps in elderly people. The dose of digoxin should be halved if quinine is prescribed, and the serum concentration checked after five days. A pharmacokinetic interaction also occurs with amiodarone to increase serum digoxin concentration.

CONTROVERSIAL TREATMENTS

β *Blockers*—These improve survival after myocardial infarction, especially in patients with evidence of severe left ventricular dysfunction.[43] In patients with more severe heart failure due to dilated cardiomyopathy cautious administration of low doses of metoprolol and prolonged follow up may benefit both quality of life and survival.[44] At present, however, prescription of β blockers is limited to a few selected patients in specialist centres.

Xamoterol—This partial β_1 adrenoceptor agonist is of symptomatic benefit in patients with mild heart failure,[45] but mortality was increased when it was given to patients with severe heart failure.[46] Its indications remain unclear and it is not widely used.

Calcium channel blockers—This class of drugs has generally been contraindicated because myocardial depression is a direct consequence of calcium channel blockade. Recently, a new dihydropyridine, amlodipine, has been shown to increase patients' effort capacity in preliminary studies.[47] However, it would be wise to await the result of a large mortality trial presently underway in the United States before recommending amlodipine for heart failure.

Points affecting management of atrial fibrillation in patients with heart failure

- Is atrial fibrillation the cause or consequence of heart failure?
- Could the patient have mitral valve disease?
- Could the patient have thyrotoxicosis?
- Is atrial fibrillation part of sick sinus syndrome? (Bradycardia may aggravate heart failure, and digoxin may aggravate bradycardia)

NON-PHARMACOLOGICAL TREATMENT

Diet—Obesity should be discouraged as this increases the workload on the heart, especially during exercise. Excess salt intake should be avoided as this may aggravate a patient's condition.

Fluid intake—Patients with heart failure often have an intense thirst, which can lead to excessive fluid intake and hyponatraemia. Fluid intake should be limited to about 2 l a day for most patients. During periods of hot weather, diarrhoea, vomiting, or fever, fluid intake may be increased or the dose of diuretic reduced.

Alcohol intake—Excessive alcohol intake can damage the myocardium and precipitate atrial arrhythmias and should be avoided.

Smoking—Smoking cigarettes causes vasoconstriction in heart failure and should be avoided for this and other reasons.

Non-compliance—Careful advice about the rationale behind treatment, especially diuretic treatment, and an explanation about flexible timing of doses may help to prevent non-compliance.

Vaccination—Heart failure may predispose to and be exacerbated by pulmonary infection, which is a common cause of hospitalisation. Therefore, influenza and pneumococcal vaccinations are recommended.

Exercise—Bed rest is an important part of the treatment of acute heart failure or decompensated chronic heart failure. Otherwise regular exercise should be encouraged as this has been shown to have significant symptomatic and other benefits in patients with heart failure.[48]

Management of concomitant problems

ATRIAL FIBRILLATION

Between 10% and 50% of patients with heart failure have concomitant atrial fibrillation.[1 18-20] Four questions should be asked before management is started (box). Control of ventricular rate is usually achieved with digoxin; if there is difficulty consider amiodarone but remember that plasma digoxin concentrations may rise. Thromboembolism should be prevented, and recent trials have shown substantial benefit of warfarin (table III).[49] Cardioversion, possibly preceded and followed by treatment with amiodarone, may be con-

TABLE III—*Results of recent trials of treatments for prevention of stroke in atrial fibrillation. From Nolan and Bloomfield*[49]

Trial	No of patients	Treatments	Follow up (years)	Annual event rate (%)		Relative risk of warfarin treatment (%)
				Placebo	Warfarin	
Atrial fibrillation, aspirin, antikoagulation	1007	Placebo *v* aspirin *v* warfarin	†	4·8*	1·4*	71
Boston area anticoagulation trial for atrial fibrillation	420	Placebo *v* warfarin	2·2	2·9	0·4	86
Stroke prevention in atrial fibrillation	1330	Placebo *v* aspirin *v* warfarin	1·3	7·4	2·3	67
Canadian atrial fibrillation anticoagulation study‡	378	Placebo *v* warfarin	1·3	3·7	2·1	43
Stroke prevention in non-rheumatic atrial fibrillation	571	Placebo *v* warfarin	1·8	4·3	0·9	79

*Overall event rate. †Not known. ‡Terminated early.

sidered in some patients who are not thought to have chronic atrial fibrillation.

ANGINA

As the commonest cause of heart failure is coronary artery disease, many patients also have angina. Coronary artery bypass grafting should be considered if the patient is otherwise suitable for surgery. Angioplasty may also be appropriate. Prognosis may be improved by surgery in patients with extensive coronary artery disease and left ventricular dysfunction (fig 6).[23] Advanced age (>75 years) and severe left ventricular dysfunction (left ventricular ejection fraction <20%) are contraindications. Until recently, the only anti-ischaemic drugs available that did not exacerbate pump dysfunction were the nitrates. Amiodarone, however, which was originally introduced in France as an antianginal drug, may also be of benefit.[50] Angiotensin converting enzyme inhibitors have a variable effect in angina and can worsen symptoms in some patients.[51]

VENTRICULAR ARRHYTHMIAS

Patients with symptoms of palpitations, dizziness, and blackouts should be investigated for arrhythmias since symptomatic ventricular arrhythmia requires treatment. Before an antiarrhythmic drug is given, possible precipitating or aggravating factors must be excluded (see box). The drug of choice is amiodarone; others are likely to exacerbate a patient's overall condition and even the arrhythmia.[50] The role of implantable pacemaker and defibrillator devices in patients with congestive heart failure is not yet clear.[52]

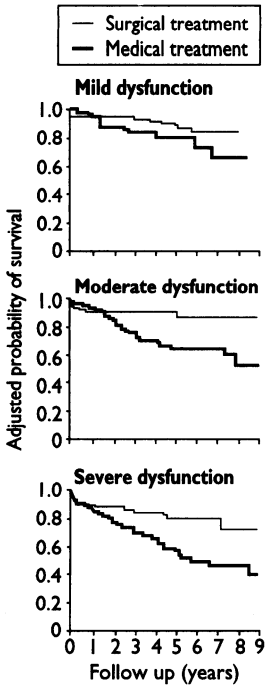

FIG 6—*Comparison of survival among patients with mild, moderate, and severe left ventricular dysfunction (left ventricular ejection fraction 38%, 32%, and 24% respectively) who were treated medically or by coronary artery bypass grafting. From Bounous et al*[23]

Possible precipitating or aggravating factors for ventricular arrhythmia

- Electrolyte disturbance (hypokalaemia, hypomagnesaemia, hyperkalaemia)
- Digoxin toxicity
- Drugs exacerbating pump dysfunction (for example, calcium channel blockers)
- Drugs causing electrical instability (for example, antiarrhythmic drugs, antidepressants)
- Recurrent myocardial ischaemia

Management of heart failure

Figure 7 summarises present management of heart failure, but several clinical trials in heart failure are due to report their findings in the next few years (table IV). Many are looking at the impact of symptomatically effective agents on mortality.

APPARENTLY INTRACTABLE CONGESTIVE HEART FAILURE

Patients who do not respond to treatment usually require hospital admission, bed rest, fluid restriction, combination diuretic treatment (often with an intravenous loop diuretic), intravenous inotropic drugs

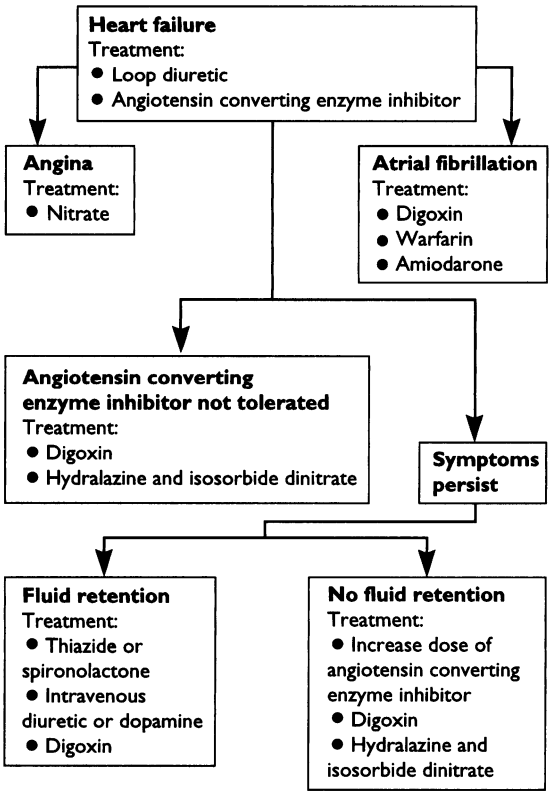

FIG 7—*Summary of management of heart failure*

(dobutamine), and low dose dopamine.[54] Invasive haemodynamic monitoring is often helpful in establishing treatment goals and efficacy. Compounding factors should be excluded (box), and if all else fails cardiac transplantation may be considered provided the operation is not contraindicated (box). Other surgical procedures such as dynamic cardiomyoplasty, implantable ventricular support devices, and total artificial hearts are still under evaluation.

IMPLICATIONS FOR FUTURE MANAGEMENT

Seven drugs used in the treatment of heart failure have been shown to increase mortality either by

Questions arising from apparently intractable congestive heart failure

- Is congestive heart failure the correct explanation for deterioration (for example, has lung cancer developed)?
- Is there a role for conventional surgery such as coronary artery bypass grafting, aneurysmectomy, or pericardectomy?
- Is there overtreatment (for example, overdiuresis with uraemia and electrolyte disturbance or digoxin toxicity)?
- Is there undertreatment (could any treatment be added or increased)?
- Is there non-compliance (for example, with drugs, diet, or alcohol intake)?
- Is there coprescribed or over the counter medication with adverse effects?
- Is there thyroid disease?
- Is there infective endocarditis?
- Is there pulmonary infection?
- Is there inappropriate bradycardia (might pacing help)?
- Is there frequent non-sustained ventricular tachycardia or frequent ventricular premature beats (would suppression help)?
- Is pulmonary thromboembolism occurring?

Adapted from Dargie and McMurray[8]

TABLE IV—*Clinical trials of treatments for heart failure due to report in near future. From Cleland*[53]

Trial	Treatment	Status of subjects (New York Heart Association class)
Digitalis Investigators Group	Digoxin *v* placebo	II and III
Prospective randomised amlodipine survival evaluation	Amlodipine *v* placebo	III and IV
Prospective randomised flosequinan longevity evaluation	Flosequinan *v* placebo	III and IV
Veterans Affairs amiodarone trial	Amiodarone *v* placebo	II, III, and IV
Group study of heart failure survival in Argentina	Amiodarone *v* placebo	III and IV
Metoprolol in dilated cardiomyopathy	Metoprolol *v* placebo	II and III
Cardiac insufficiency bisoprolol study	Bisoprolol *v* placebo	II and IV
Veterans heart failure trial III	Felodipine *v* placebo with and without digoxin	II and III
Prospective randomised ibopamine mortality evaluation	Ibopamine *v* placebo	II and III
Xamoterol	Xamoterol *v* placebo	III and IV

TABLE V—*Large ongoing trials of angiotensin converting enzyme inhibitors for treatment of myocardial infarction*

Trial	Treatment	Expected study size (thousands)	Principal outcome	Expected completion
Fourth international study of infarct survival	Captopril *v* placebo, isosorbide mononitrate *v* placebo, and randomised open label magnesium	40-50	At five weeks and long term mortality	1993
Gruppo Italiano per lo studio della Sopravvivenza nell'Infarto Miocardico[14]	Lisinopril *v* placebo and isosorbide mononitrate *v* placebo	20	Short term mortality and clinical congestive heart failure	1994-5
Acute infarction ramipril efficacy	Ramipril *v* placebo	2	Mortality and congestive heart failure	1993
Trandolapril cardiac evaluation	Trandolapril *v* placebo	1·5	Mortality and congestive heart failure	1993-4

worsening pump function or by increasing the rate of sudden death. These drugs are dobutamine,[55] milrinone,[21] enoximone,[56 57] xamoterol,[46] flosequinan (letter to doctors from Boots Pharmaceuticals, 17 July 1993), vesnarinone (at high dose),[58] and a new prostaglandin analogue, epoprostenol (letter to investigators from Wellcome Foundation, 18 June 1993). Several of these drugs possess inotropic activity, and this has been suggested as a possibly unsuitable pharmacological action for future drugs for heart failure. Recently, however, vesnarinone, a new inotropic drug with phosphodiesterase inhibitory action, has been shown to reduce mortality and improve quality of life at low doses whereas it increased mortality at high doses. The adverse effects of flosequinan (whose minor degree of phosphodiesterase inhibition was not thought to be clinically important) and epoprostenol are of possibly greater concern since these drugs were thought of as primarily vasodilators.

Clearly, better targeting of drugs in patients with different types of heart disease is needed in future. The term heart failure is insufficiently informative about the underlying mechanisms. Its investigation and management are unsatisfactory: this malignant condition requires careful initial scrutiny in a specialist unit. Follow up might best be achieved by developing shared care strategies with general practices and expanding the role of specially trained liaison nurses in the community. Many of the present admissions to hospital for heart failure could be prevented by giving attention to the detail of heart failure management.[6]

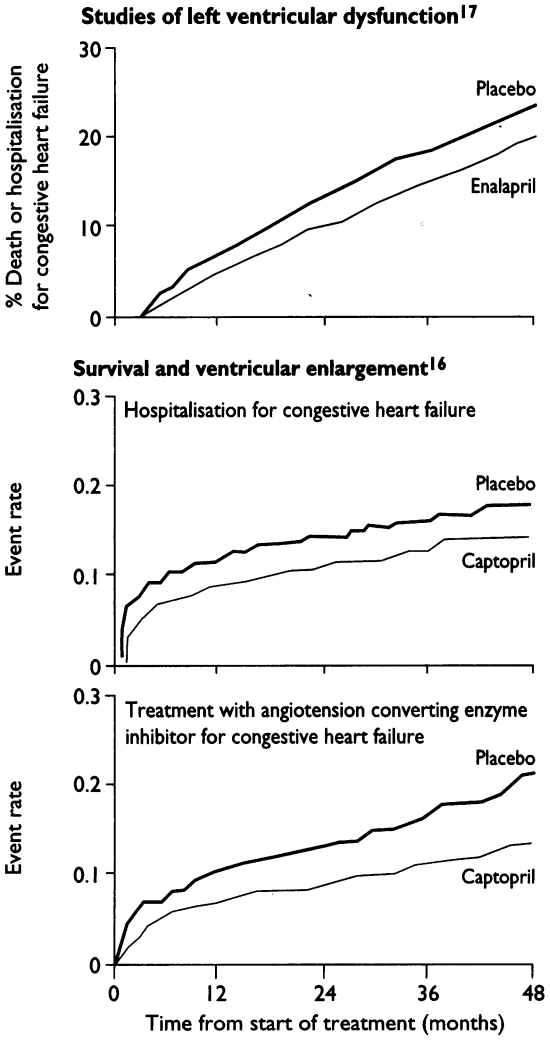

FIG 8—*Effects of angiotensin converting enzyme inhibitors on hospitalisation or development of heart failure in patients with left ventricular dysfunction*

Standard contraindications to cardiac transplantation

- Advanced age
- Fixed pulmonary hypertension
- Poor renal function (glomerular filtration rate <30 ml/min)
- Parenchymal lung disease
- Pulmonary infarction
- Hepatic disease
- Continuing peptic ulceration
- Peripheral and cerebrovascular disease
- Malignant disease
- Insulin treated diabetes mellitus (some centres)
- Other severe disease likely to limit rehabilitation
- Drug or alcohol addiction
- Severe psychiatric disease
- Probable non-compliance with treatment

Adapted from Dargie and McMurray[8]

Prevention of heart failure

Since the burden of symptoms is high and prognosis poor in established heart failure, prevention is highly desirable and can now be realised in high risk patients. In a trial of 4228 patients with asymptomatic left ventricular dysfunction,[17] subjects who received enalapril had, after a mean follow up of three years, a 37% reduction in the risk of developing heart failure compared with controls who received placebo (fig 3) and a 36% reduction in the number of first hospitalisations for heart failure (fig 8). Similarly, in a study of 2231 patients with left ventricular dysfunction who received either captopril or placebo after a myocardial infarction,[16] those given captopril had, after a follow up of 3·5 years, a 37% reduction in the risk of developing heart failure and a 22% reduction in the risk of requiring hospitalisation for heart failure (fig 8). In both these studies there was a significant reduction in recurrent myocardial infarction and in unstable angina. Many suggestions have been made to explain this, including the lowering of blood pressure and greater plaque stability.[59] Additional trials are presently exploring the potential role of angiotensin converting enzyme inhibitors in patients with myocardial infarction (table V). Recently, ramipril has been shown to improve prognosis in high risk patients after an acute myocardial infarction (that is, those with clinical evidence of heart failure).

Conclusions

The diagnosis and management of heart failure are rapidly changing. Interest is focusing on the early identification and prevention of progression of left ventricular dysfunction (the provision of easy direct

access to echocardiography for general practitioners is crucial to this); the concept of viable myocardium and the scope for revascularisation in the context of poor left ventricular function due to coronary heart disease; and new surgical techniques apart from transplantation for end stage heart failure.

It must be remembered that many of the patients who took part in trials only a few years ago have since died and that many patients and their relatives endured several very uncomfortable months. For such patients, in the absence of transplantation, the overriding issue is the quality of the end of their life. We have been preoccupied with quantity of life and have demanded a positive mortality end point for our new drugs. Although even a small decrease in survival is important, the issue of quality versus quantity in end stage heart failure requires urgent discussion as more patients survive the earlier stages of this malignant disease.

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