Congestive heart failure
Towards a comprehensive treatment

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Heart failure constitutes an increasing health hazard with major demands on health care resources. Recent major advances in drug treatment have yet to be translated into increased survival of heart failure patients in the community at large. Failure of diagnosis is a major factor in delaying early and adequate treatment. Echocardiography probably provides the most reliable and inexpensive instrument to confirm the diagnosis and pinpoint the mechanical components of the syndrome.

The targets for therapeutic intervention may be categorized (i) haemodynamic, neuroendocrine and metabolic disorders (ii) symptoms and quality of life, (iii) morbidity and mortality risks. Symptoms and quality of life are the prime concerns of the physician in the treatment in the individual patient. Selection of anti-heart failure drugs used should be based on knowledge of the impact on the pathophysiological disorders and on the morbidity and mortality risks.

Diuretics, vasodilators and ACE-inhibitors are now accepted as standard treatment, particularly when used in combination. Controversy continues to surround the efficacy of digitalis glycosides; they improve symptoms in some patients but their impact on morbidity and mortality risks is still uncertain. Even with standard treatments, may practical therapeutic questions remain, one of which is what is the most efficacious dose of each anti-heart failure drug which, when used in combination, will give the maximum improvement in quality of life and greatest extension of survival? Despite available treatment with diuretics, digitalis, vasodilators and ACE-inhibitors, the morbidity and mortality risks of congestive heart failure remain high. None of these drug groups significantly modulates the excessive excitation of the sympathoadrenal system, one of the two major neuroendocrine hazards of heart failure. For this reason, amongst the many newer drugs in development, the beta-adrenoceptor antagonists hold considerable promise as the next step towards a more comprehensive treatment of congestive heart failure.

(Eur Heart J (1996); 17 (Suppl B): 43-56)

Key Words: Congestive heart failure, diagnosis, treatment, symptoms, survival.

Introduction

Knowledge of the basic pathophysiological processes and the mechanisms whereby they induce the clinical expressions of heart failure continues to increase, spurred on, not only by the development of new drugs, but also by increasing refinement of methods of evaluating their efficacy. In recent years, the major clinical interest in this field has centred on the results of formal large-scale survival trials many of which — with various drugs, to a varying extent, and in a variety of patients — have demonstrated a reduction in the overall mortality risk. However, the hopes they raised must be tempered by the widening gap between the knowledge so gained and its application to the treatment of the individual patient in heart failure. The evidence suggests that maximum therapeutic benefit in terms of amelioration of symptoms, improvement in quality of life, reduction in morbid events and extension of life-span is achieved in only a small number of such patients. Moreover, the advances made in large-scale clinical trials have yet to be translated into a longer life-span in the population at risk in the community at large (Fig. 1). Heart failure now afflicts over 1% of the general population and nearly 1 in 10 of the elderly and is continuing to increase in frequency in most industrial societies (Fig. 2). This places considerable demands on the physician and other health-care resources; 5% of all hospital admissions are for heart failure and 1 in 3 patients are re-admitted within a year of discharge. Overshadowing all other considerations, however, is the severe and detrimental impact of the symptoms of heart failure on the quality of life of the patient.

The prime objective of the majority of trials of drug therapy in chronic heart failure has been directed
to their effects on survival but the gains in life-quality so far recorded in the various trials have been less than impressive. The impact of therapy on mortality risk is of prime concern in the global evaluation of drug therapy, but the physician facing the individual patient with heart failure can only be concerned with the impact of treatment on symptoms and overall quality of life of the patient. Whether such treatment will prolong their life or fail to do so will never be known in the case of the individual. For this reason, it is beholden not only to re-examine continually and critically new pharmacotherapeutic information derived from formal clinical trials, but also to determine how far such information may be applied to the far broader populations met in practice than those specifically selected for finite clinical trials.

The ultimate treatment undoubtedly resides in prevention, but this is unlikely to reverse the increasing incidence of heart failure in the foreseeable future. The physician will therefore still have to contend with a syndrome which will come to his notice only when the patients presents with symptoms i.e. at a relatively late stage of the syndrome in life-span terms. The earlier that heart failure is detected with certainty, the better the prospects for retarding its natural history by optimum treatment and, thus, the amelioration of symptoms and prolongation of survival[2,3]. The first consideration, therefore, is the precision of the diagnostic detection of heart failure in routine clinical practice.

**Diagnostic dilemmas in heart failure**

The clinical diagnosis of heart failure in the later stages of the syndrome is both highly specific and highly sensitive. For the experienced physician, the presence of the symptoms of breathlessness and fatigue, together with the clinical signs of raised jugular venous pressure, pulmonary congestion, tachycardia with gallop rhythm, hepatomegaly and angle oedema are of sufficient diagnostic validity to require little further evaluation. In
earlier stages of heart failure, however, when symptoms are likely to be nonspecific and accompanied by a dearth of physical signs, the clinical diagnosis is more open to fault and often missed. Studies in general practice have disclosed that the diagnosis of heart failure may be in error in up to 50% of the patients, even in those with symptoms\(^4,5\). Moreover, there is widespread under-investigation of patients with possible heart failure in this environment\(^6\). The most reliable and relatively inexpensive investigation to confirm the diagnosis of heart failure, at least in patients with cardiac dilatation at rest, is undoubtedly provided by the echocardiogram\(^7\). It is also useful to describe the mechanical components of the syndrome, namely systolic or diastolic dysfunction, which are difficult to differentiate solely on the basis of clinical signs and symptoms\(^8,9\). Diuretics, positive inotropes, vasodilators and ACE-inhibitors are particularly useful in patients with predominant systolic dysfunction. In contrast, beta-blocking drugs and calcium antagonists are of prime value in diastolic dysfunction, the former augmenting diastolic filling by slowing the heart rate and the latter by enhancing myocardial relaxation. Echocardiography not only furnishes a valid and reliable confirmation of the diagnosis of established heart failure but also provides a ready instrument to monitor therapeutic progress\(^10\). Unfortunately, its clinical utility in this regard is still not widely appreciated, accounting for its under-utilization in open general practice\(^11\).

**Therapeutic objectives in the treatment of heart failure**

The pharmacotherapeutic targets in heart failure must be considered in relation to the natural history of the syndrome (Fig. 3)\(^12,13\). Damage to the heart muscle or work overload of the heart is immediately countered by intrinsic changes in the myocardium which attempt to sustain contractile activity. Initially, increased stretch of the cardiac myocytes enhances their sensitivity to cytosolic calcium and augments their contraction. However, if overstretching is maintained, the reuptake of calcium by the sarcoplasmic reticulum is progressively impaired with dire consequences not only for the contractile activity of the myocyte but also for its electrical stability\(^14,15\). At this point, when the failing ventricle cannot maintain its output without permanent increases in volume and pressure, many neuroendocrine reflexes are alerted, but predominantly those employing the sympathoadrenal system and renin-angiotensin-aldosterone axis\(^16,21\). Sympathoadrenal stimulation of the heart is at its most intense in the earliest stages of heart failure, but the results of such stimulation are rapidly attenuated by the failure ('down-regulation') of myocardial beta-adrenoceptors\(^22\). The role of angiotensin is also complex. The direct and indirect functional consequences for the failing heart as a result of genetically determined differences in angiotensin-converting enzyme activity due to the possession of the deletion genotype (DD) are still unclear\(^23\). From the clinical viewpoint, however, in the earliest stages of heart failure, heightened neuroendocrine activity may be sufficient to maintain the pumping performance of the damaged heart. Eventually however, myocardial failure progresses inexorably to the point at which, despite both the intrinsic cardiac adaptations and the extrinsic neuroendocrine activation, the pumped output of the heart is incapable of maintaining circulatory integrity and nutritional supply of the metabolically active tissues. These pathophysiological developments translate into distinct, if overlapping, stages in the clinical presentation and hazardous consequences of heart failure. In the earliest stages, (New York Heart Association
Classification I and IIa), with a paucity of symptoms or signs, the immediate clinical hazards are small, although firmly predictive of the future progression of the syndrome. In the stage when cardiac dilatation and symptoms ensue during exercise the main threat is that of electrical instability of the damaged and overstretched myocardium and the precipitation of life-threatening arrhythmias (NYHA Class IIb and IIIa). In the terminal stages of the syndrome, when symptoms are present even at rest, the heart is grossly dilated and accompanied by all the traditional peripheral signs of ‘congestive heart failure’ (NYHA Class IIIb and IV).

The mechanisms responsible for the symptomatology of the syndrome are complex and complicated by the fact that symptoms in patients with heart failure may not quantitatively correlate with changes in the haemodynamic, neuroendocrine or metabolic profiles of the patient and there is wide and unpredictable variability between these profiles and symptoms between patients. The cardinal symptom of patients with congestive heart failure is their restricted exercise capacity which is primarily limited by breathlessness during fast exercise and by fatigue during slow exertion. The sensation of breathlessness is accompanied by an abnormal increase in ventilation at any workload and at any level of carbon dioxide production. The increased ventilation helps to maintain normal systemic arterial oxygenation despite pulmonary congestion and increased dead space. The sensation of breathlessness is closely correlated with changes in the pulmonary vascular pressures. It is also complexly associated with lung water, compliance and dead space and the increased work of the respiratory muscles in terms of both force and rate, although the exact relationships and mechanisms involved remain to be clarified. In contrast, fatigue is due to a wide variety of discordant disorders including deconditioning of striated muscle, short-stepping gate, changes in the striated muscle and the micro-circulation, defective utilization of muscle metabolic substrates and elevated energy expenditure even at rest. Above all, the relationship of such symptoms to the patients routine life-style adds a factor that only the individual physician can utilize to evaluate the impact of drug therapy.

Many trials are now investigating the influence of drugs in the earlier stages of heart failure, but in these studies the objectives are primarily concentrated on lengthening life-span. But in the later stages of the syndrome the prime objective of therapy is the amelioration of symptoms (Fig. 4). This overview will therefore concentrate on the goals of drug therapy and the clinical expectations of treatment in the later symptomatic stages of the syndrome.

**Major objectives of therapy**

The first major objective of pharmacotherapy in the patient in heart failure is correction or amelioration of the haemodynamic, neuroendocrine and metabolic disorders present, all of which are important determinants of the ultimate prognosis. Fortunately, the group results of formal clinical trials of drug therapy are sufficiently uniform for the practising physician to assume with reasonable certainty the pharmacodynamic activity of the anti-failure drugs prescribed.

The second major objective in the treatment of heart failure is the reduction in the high morbidity and mortality risk of the syndrome. This has been the subject of a number of pivotal trials. But, however attractive the results of large-scale group trials of anti-heart failure drugs, they impose considerable limitations when attempting to apply them in clinical practice. Patients included in formal prospective survival trials are often highly selected and there is usually insufficient statistical power to validate sub-group analysis. Thus the number of patients who particularly benefited, and as importantly, the patients who did not benefit or who were disadvantaged by the drug treatment under test, remains unclear. This is highlighted by the fact that many studies have included patients with widely different degrees of disability so that the averaged improvement is difficult to apply to any particular individual. The majority of trials have also been relatively short-term, particularly when one considers the relative longevity of patients with less severe heart failure. Ideally, the practising physician should attempt to mimic these results by matching his patients with those included in the published trials and use the same medications and dosages. However, it is over-ambitious to expect that at best more than a few physicians will adhere to such severe limitations on their clinical practice, particularly when it is realized that it will never be known if a treatment prolongs or shortens life in the individual patient.

The third major, and most important, therapeutic objective for the practising physician is the amelioration of symptoms and improvement in quality of life of the individual patient with congestive heart failure. This overriding practical objective of drug treatment is rarely given the attention it warrants. Just as it would be inconceivable to use drugs that had not been shown to have measurable effects on one or more of...
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Figure 5 A perspective for adjudging clinical impact of drug therapy in heart failure.

Figure 6 Schematic summary of the results of large scale trials of drugs in patients in severe heart failure in terms of the inter-relationship of their impact on quality of life and life-span; for explanation see text.

the prime pathophysiological disorders in heart failure, so it would be clinically reprehensible to use drugs which could not be expected to improve a patient's symptoms.

Considered against this background, there are three ways by which the efficacy to the treatment of congestive heart failure may be monitored: by haemodynamic improvement, by attenuation of the heightened neuroendocrine activity, and by improvement in the patients symptoms and quality of life. Under the usual conditions of clinical practice, it is only the latter avenue of persistent monitoring which is possible. However, amalgamating the information from survival trials with that directly obtained from the clinic, may crystalize for the physician the benefits of each drug treatment he or she may expect in the patient with congestive heart failure (Fig. 5). This overview will be particularly devoted to this specific aspect, namely the impact of drug treatments on symptoms and survival prospects of patients with congestive heart failure.

Drug treatment of congestive heart failure

Traditional treatments most widely used in the treatment of heart failure comprise diuretics, digitalis glycosides, vasodilators and ACE-inhibitors. Although confirmation is awaited from other large-scale trials in progress, the positive results of the GESICA (Grupo Español para el Seguimiento del Injerto Coronario) Trial also suggest that the anti-arrhythmic amiodarone should now be considered for inclusion in the routine drug treatment of the syndrome[49]. Although it is still undecided at what stage each drug should be commenced, there is little doubt that in the later stages of the syndrome (NYHA Classes III and IV) all five classes of drugs should be prescribed if the patient can tolerate them (Fig. 6). Multi-drug therapy has been shown to extend life-span in many patients in a number of large-scale prospective randomized clinical trials[42-49], but these trials have given no information on the most efficacious balance of drug doses to be used. Likewise, there is no information on the proportionate effectiveness of different individual anti-heart failure drugs in relieving symptoms, as multi-drug therapy is the rule both in practice and in clinical trials. The final prescription can only be decided by the physician in each individual patient and only determined from the impact of such therapy on their symptoms.

Diuretics

There is a sound theoretical and practical basis for the use of diuretics in the treatment of heart failure[50-55]. The increased diuresis and consequent reduction of the expanded blood volume is accompanied by improvement in cardiac pumping performance due to the reduction in both preload and afterload[56,57]. Although never formally compared, it would appear that the thiazides and loop diuretics produced directionally similar haemodynamic changes which are maintained during dynamic exercise[57-59]. Diuretic stimulation of renal renin release and subsequent activation of the vasoostrictor angiotensin and salt-retaining aldosterone may occur when large doses of diuretics are used, although this appears to be less of a problem in the elderly heart failure patient than in a younger subject[20]. This is probably of little clinical importance, however, as both potentially adverse effects are completely countered by the ACE-inhibitors that the majority of patients with congestive heart failure are prescribed[51]. Diuretics acting on the ascending limb of the loop of Henlé in the nephron have long been the drug of choice in the treatment of heart failure. Thiazides, are however, no less efficacious. Contrary to some clinical opinions, it is
now clear that a combination of small doses of diuretics acting on different parts of the nephron are more efficacious in terms of salt and water excretion than larger doses of a single compound\textsuperscript{[60]}. The combined prescription of small doses of different diuretics also precludes the development of diuretic resistance to a single drug\textsuperscript{[61]}. The clinical utility of the diuretics has been greatly extended by the development of compounds with high absorption, high bioavailability and long duration of action\textsuperscript{[62]}.

The diuretics have undoubtedly achieved their pre-eminent first-line role in the treatment of heart failure based solely on their ability to relieve symptoms in the majority of patients to whom they are administered. In this regard they are the equal, or even superior to all other currently available anti-heart failure drugs including the ACE-inhibitors\textsuperscript{[63]}. The diuretic-induced improvement in symptoms is invariably associated with a substantial diuresis which is certainly the predominant and perhaps sole mechanism by which the diuretics attenuate symptoms and improve quality of life\textsuperscript{[64]}. A number of recent clinical trials have clearly defined the benefits of diuretics on the symptom profile of patients with congestive heart failure. The majority of information stems from studies with loop-diuretics. A double-blind trial with the loop diuretic torasemide (5 or 10 mg daily in 119 patients with congestive heart failure) demonstrated a significant improvement in symptoms and clinical signs during 48 weeks of sustained treatment\textsuperscript{[62]}. Another double-blind placebo-controlled clinical trial of 4 weeks with the same loop diuretic also demonstrated a significant improvement in symptoms of breathlessness and peripheral oedema although cardiomegaly and hepatomegaly were less amenable to treatment (Fig. 7)\textsuperscript{[65]}. A double-blind randomized parallel design study in 120 patients with mild and moderate heart failure treated with either furosemide or torasemide demonstrated a significant improvement in their symptomatic disability as judged by the New York Heart Association Functional Classification (From\textsuperscript{[66]}, reproduced with permission. ■ = better; ● = unchanged; n = 151).

Figure 7 Improvement in symptoms in patients with chronic heart failure after 4 weeks treatment with torasemide 5 or 10 mg daily. (From\textsuperscript{[65]}, reproduced with permission).}

Figure 8 Results of 4 weeks treatment with torasemide 5 or 10 mg daily related to severity of heart failure assessed according to New York Heart Association Functional Classification (From\textsuperscript{[66]}, reproduced with permission. ■ = better; ● = unchanged; n = 151).

symptoms as surrogate representatives for changes in quality of life. On this basis there is little doubt that diuretics have a major impact on improving quality of life in patients with chronic heart failure which is inversely related to the severity of the clinical syndrome (Fig. 9).

No major trial has been directed to ascertaining the influence of diuretics on the morbidity and mortality risks of patients in severe heart failure (NYHA class III and IV). It is unlikely that such studies will be undertaken considering that diuretics are so firmly established as first-line drugs in symptomatic heart failure that the majority of physicians would find it ethically unacceptable for diuretics to be excluded from any treatment group. Although there is no substantive clinical trial evidence that diuretics reduce morbidity and extend survival of patients with congestive heart failure, it should be remembered that in all the major survival trials in heart failure so far undertaken many of the patients in all arms of the various trials received diuretics as well as the drug under test.

**Positive inotropes**

For many physicians, digitalis glycosides together with the diuretics, continue to remain a mainstay of the treatment of symptomatic heart failure. The symptomatic benefits conferred by digitalis may be less clear-cut than those induced by the diuretics but this may be due to their nearly universal combined prescription. No formal large-scale clinical trial has been mounted to question this point and a number of smaller studies have not shown completely convincing evidence of the symptomatic benefits of digitalis therapy. Some studies have indicated that the addition or withdrawal of digitalis has led to clinical improvement or deterioration, respectively. A major pharmacotherapeutic drawback of digitalis is its narrow dose-response relationship so that the fixed-dose selected in order to avoid toxicity often falls short of the effective therapeutic range.

The effects of the digitalis glycosides on morbidity and mortality risks of patients with symptoms of heart failure is unknown, but is now the subject of a major clinical trial in North America in combination with diuretics, vasodilators and ACE-inhibitors. Should the trial results indicate no particular prognostic benefits, but no harm, then physicians will be left to make the difficult individual decision as to whether to prescribe digitalis instead of the potential symptomatic benefits it may afford. They may be influenced in this regard by the finding that in a number of small studies the digitalis glycosides improved patients feelings of well-being more than either placebo or even ACE-inhibitors (Fig. 10). But the future clinical popularity of the digitalis glycosides will undoubtedly be greatly influenced by the outcome of the large scale survival trial being undertaken in North America.

Many drugs with positive inotropic activity have failed formal survival trials. However, a number have clearly demonstrated a beneficial impact on symptoms and quality of life of patients with severe congestive heart failure despite the failure to prolong survival. However, none has yet achieved sufficient overall efficacy to be accepted into clinical practice, which leaves the digitalis glycosides as the only positive inotrope than is widely prescribed for heart failure.

**Vasodilators**

The introduction of the vasodilator era, some 25 years ago, constituted the second major advance in the treatment of heart failure of recent times. Their haemodynamic effectiveness and clinical efficacy in patients...
with heart failure is now beyond question. However, the term 'vasodilators' encompasses a wide range of different pharmacological groups which have widely diverse activities in the peripheral and central circulations. These range from the earliest alpha-1 adrenoceptor antagonists through such groups as the direct acting peripheral vasodilators, nitrates, hydralazine and minoxidil and other imidazolines, the slow calcium-channel antagonists which only dilate the systemic arteriolar resistance vessels, dopaminergic agonists such as ibopamine, atrial natriuretic peptide inhibitors such as candesartan, flosequinan, with combined arteriolar and venodilator activities, and potassium-channel activators with similar combined vasodilator effects. Many drugs which dilate the systemic resistance and capacitance vessels also have other significant circulatory activities. For example, flosequinan has some direct positive inotropic activity, the calcium antagonists have negative inotropic effects and ibopamine has diuretic activity. Thus, the vasodilators comprise a heterogenous group of drugs with the only common property being dilatation of the vessels of the systemic vascular system. All vasodilators have the universal property of reducing cardiac afterload and/or the preload. Some, such as the nitrates, have dose-dependent activity; at low doses nitrates dilate the systemic venous capacitance system and in high doses also dilate the arterial resistance vessels. As a heterogenous group, vasodilators improve the haemodynamic profile of the patients with heart failure but their individual effects on the neuroendocrine and metabolic profiles are less well documented.

The majority of vasodilators have been shown to attenuate symptoms and improve exercise capacity to a greater or lesser extent in patients with symptomatic heart failure. In many the effects are dose-dependent and with many, pharmacodynamic tolerance is a problem, e.g. nitrates, alpha-1 adrenoceptor antagonists. Moreover, many induce side-effects, particularly hypotension, and particularly in the elderly. There are few formal studies of the influence of any of the vasodilators on the quality of life of patients with heart failure. This makes it difficult to predict the impact of the addition of a vasodilator to other anti-heart failure treatments of the quality of life of a patients with symptomatic heart failure. There is some evidence, however, from two large-scale studies, that additional clinical benefit may be expected when a direct-acting vasodilator such as flosequinan is added to conventional treatments including ACE-inhibitors.

The influence of vasodilators on morbidity and survival has been the subject of two large-scale studies. The first, a placebo-controlled comparative trial, unequivocally demonstrated that fixed doses of hydralazine and isosorbide dinitrate (ISDN) added to diuretics and digitalis extended life-span in patients with moderate congestive heart failure (NYHA III) compared to placebo, although alpha-1 adrenoceptor blockade with prazosin did not (Fig. 6). A more recent multi-centre placebo-controlled trial with two doses of flosequinan demonstrated no improvement in survival with either dose and the trial was prematurely terminated with the higher dose of drug used resulted in increased mortality risk. Thus it would appear that irrespective of their ability to induce an improvement in the haemodynamic profile and, in many instances, improvement in patients' symptoms, it cannot be assumed that all drugs with vasodilator activity will increase the life-span of patients with symptomatic heart failure. This can only be ascertained by subjecting each drug to a rigorous formal clinical trial.

There are two aspects of particular clinical importance from the practical viewpoint. The V-HeFT I trial demonstrated some extension in life-span for the group of patients as a whole, but the sample size of patients precluded the demonstration of benefit or disadvantage of treatment in any particular subgroup defined by age, gender, aetiology or other objective variable. A practical therapeutic drawback in applying the result of the V-HeFT I trial is that vasodilators hydralazine and ISDN were given in a fixed dose, a prescription which may not be suitable for all patients, particularly the elderly.

ACE-inhibitors

The introduction of the ACE-inhibitors was the third major drug development which has done much to revolutionize the treatment of congestive heart failure in recent years. They are considered an obligatory addition to diuretics in the drug therapy of congestive heart failure for a number of reasons. They improve left ventricular pumping performance by directly reducing left ventricular afterload through dilatation of the systemic arteriolar resistance vessels. How much of this dilatation results from reduction of circulating angiotensin-II and how much from reduction of angiotensin in the vascular wall is unknown. These direct vasodilator effects are augmented by (a) the reduction of sympathoadrenal activity which is a result of modulation of the central vasomotor centre tone responsible for sympathoadrenal discharges; and (b) blocking angiotensin-II receptors in sympathetic nerve terminals responsible for enhancing the release of noradrenaline. The ACE-inhibitors are also of direct clinical utility in that they blockade one of the major disadvantages of concomitant treatment with diuretics, namely the release of renin and activation of angiotensin-II and later the increased stimulation of aldosterone release. During long-term administration the ACE-inhibitors can also be expected to reduce left ventricular hypertrophy, particularly in patients with the ACE gene deletion allele. ACE-inhibitors undoubtedly improve symptoms and quality of life in patients with severe heart failure (Fig. 6). However, in many instances, these benefits are relatively modest and less than that achieved with diuretics. ACE-inhibitors have all been shown to improve exercise capacity but in none of the reported studies did the patients' exercise tolerance return to normal.
Undoubtedly however, the major clinical interest in the use of ACE inhibitors in heart failure resides in their ability to improve morbidity and mortality risk in patients with moderate and severe heart failure\cite{42-48}. The major improvement in mortality risk exerted by the ACE-inhibitors is predominantly related to retardation of the progression to terminal heart failure; the risk of sudden death, a major contributor to death in patients with severe heart failure appears to be little influenced by ACE-inhibitor treatment. The various mechanisms by which the ACE-inhibitors retard the progression of heart failure remains to be clarified but certainly involves remodelling of the ventricular myocardium, improvement in peripheral blood flow, reduction in sympathodrenal tone and many other synergistic influences. In patients with heart failure the ACE-inhibitors captopril and ramipril have been demonstrated to reduce significantly the risk of further coronary events. This is of crucial importance considering that in patients with congestive heart failure the incidence of myocardial infarction is increased by up to six times\cite{11}. All ACE-inhibitors are effective in improving symptoms in patients with congestive heart failure particularly when used in combination with other anti-heart failure drugs, e.g. the diuretics. Side effects, particularly hypotension and non-productive cough, limit their prescription in a small proportion of patients and with the drugs currently available there is no cross-independence of either efficacy for adverse reactions. Despite the fact that ACE-inhibitors cannot be tolerated in all patients with congestive heart failure, together with the diuretics, they form the first-line drugs of choice in the majority.

From the theoretical viewpoint a number of major issues await solution. There is increasing evidence that in some patients with congestive heart failure there is a gradual escape from ACE-inhibition with time. Whether this is a universal phenomenon, whether it is due to too small dose or poor compliance, or whether it affects only a particular patient subgroup is unknown. The optimum dose to prolong survival is also unknown and it is also unclear whether the effect on survival is age-dependent. For the practising physician these issues are of importance but only of theoretical interest. Current evidence would suggest that ACE-inhibitors should be prescribed, in combination, with diuretics in the highest dose the patient with heart failure can tolerate without side-effects. Unfortunately, although the majority of physicians are aware of the improvement in survival prospects in heart failure afforded by ACE-inhibitors, it is only a minority of patients that are afforded such treatment, at least in the United Kingdom\cite{84} and many are treated with doses outside the range associated with a reduction in mortality risk\cite{85}.

**Anti-arrhythmics**

The efficacy of anti-arrhythmic drugs in the treatment of heart failure has long been a matter of contention. In congestive heart failure, ventricular arrhythmias are frequent and associated with increased mortality risk\cite{86}. Sudden death is a cause of demise in perhaps one in three patients with congestive heart failure. Doubts were raised about the role of anti-arrhythmic drugs in the routine treatment of heart failure by the results of the CAST trial\cite{87}. The GESICA trial, however, clearly points to the potential benefit specifically of amiodarone in the routine treatment of severe heart-failure\cite{49}. In this prospective randomized trial in which amiodarone was added to diuretics, digitalis and ACE-inhibitor, the drug significantly reduced mortality. Further confirmatory studies are undoubtedly essential, and a further large-scale multicentre trial is now underway in Europe (EMIAT) to address this point albeit in post-infarction patients\cite{88}. The results of the GESICA trial taken together with the results of many smaller studies, are persuasive enough for the physician to consider the prescription of amiodarone in all patients with symptomatic heart failure (NYHA Class III and IV) (Fig. 6). Unexpectedly, in the GESICA trial, there was a significant improvement in the functional capacity of the patients on amiodarone, the reasons for which are obscure\cite{49}.

**Pharmacotherapy of heart failure — the next step**

Whatever their impact on the various surrogate endpoints of improvement, such as the haemodynamic, neuroendocrine and metabolic profiles, the final arbiters of acceptance of a drug for the treatment of heart failure are its ability to improve symptoms and quality of life, and extend lifespan. Many compounds have been developed or the treatment of heart failure, and many have improved various aspects of the haemodynamic, neuroendocrine, metabolic and symptom profiles of patients in heart failure. Such preliminary studies in small groups of highly selected patients are essential to define the initial pharmacotherapeutic potentials of a compound but they can never replace formal survival trials. Only when such studies are completed and the drug in question has been shown beyond reasonable doubt to extend lifespan, can it be recommended for universal prescription in the treatment of heart failure. However, this should never preclude the individual physician's decision to use a drug in the terminal phase of heart failure which may improve the patients symptoms without guarantee that it will extend life-span.

The drug treatment of congestive heart failure has undergone substantial evolution during the past few years but when considered in the overall context of the high mortality risk of the syndrome, despite such treatment, there is much further to go (Fig. 11). Many drugs are now under scrutiny and opinions differ as to those which hold most promise — certainly few will become established in the routine drug treatment of heart failure. Those under test embrace many novel pharmacological approaches targeted at specific pathophysiological
disorders in heart failure. The heightened activity of the sympathoadrenal system furnishes one of the two major neuroendocrine targets for therapy in heart failure, particularly as it carries such sinister prognostic implications\(^{89}\). For this reason, beta-adrenoceptor antagonists, long regarded as totally contra-indicated, are now amongst the major contenders for acceptance in the drug therapy of congestive heart failure. There are a number of theoretical and practical reasons for this change in cardiological opinion. It is now recognized that however vital in the acute situation, chronic sympathetic stimulation of the failing heart is deleterious not only from the direct mechanically induced oxygen-wasting effects, but also from the electrical instability precipitated by such stimulation. Excessive stimulation also results in progressive deterioration of myocardial beta-adrenoceptor sensitivity, which leads to diminishing inotropic support of the heart. Chronically raised plasma catecholamines are also directly injurious to the myocardium; such sympathetically induced cardiomyopathy almost certainly involves calcium overload\(^{85}\) and the generation of harmful free radicals\(^{91}\). These sympathetically mediated hazards to the failing heart may obviously be countered by beta-adrenoceptor blockade, particularly non-selective blockade of both beta-1 and beta-2 receptors. At a practical level the correction of myocardial wall asynergy and high heart rate, and suppression of release of renal renin by beta-blockade, may all contribute to benefit in the patients with heart failure. Sympathoadrenal activity is probably also intimately involved in the genesis of life-threatening ventricular arrhythmias particularly, in patients with coronary heart disease\(^{82}\). Ventricular tachycardia is common in ischaemic heart failure and sudden death accounts for more than a third of the deaths in heart failure\(^{93}\); beta-adrenoceptor antagonists are an obvious remedy\(^{94}\). These many facets of sympathoadrenal stimulation of the heart may mean that beta-blockade has an important role to play in attenuating these potentially deleterious consequences of heart failure. Moreover, coronary heart disease is by far the commonest cause of congestive heart failure in Western society, and sub-group analysis of post-infarction beta-blocker trials has shown that the greatest reductions in mortality were seen in patients with clinical evidence of heart failure\(^{95,96}\).

The evidence from clinical studies impressive if not entirely conclusive. The majority of the randomized double-blind, controlled studies have demonstrated haemodynamic improvement, and in many an improvement in symptoms and exercise capacity was recorded although neither of these surrogate endpoints was
substantial[97–99]. Although the many studies reported differed in design, beta-blocking drug prescribed, duration of treatment and patient characteristics, they fairly consistently demonstrated an improvement in symptoms and exercise capacity, and attenuation of the elevated neuroendocrine profile. Moreover, the late withdrawal of beta-blockers usually resulted in clinical and haemodynamic deterioration[100–101].

There are, however, two major hurdles to be overcome before these drugs can be advised or the routine treatment of patients with heart failure. First, no large-scale valid clinical trial has demonstrated beyond reasonable doubt that beta-blocking drugs improve symptoms and quality of life and do not incur serious side-effects in some sub-groups of patients with congestive heart failure. Second, their impact on morbidity and mortality risks are unproven. In the BHAT post-infarction trial the greatest reductions in mortality were seen in patients with mild or moderate heart failure but the trial specifically excluded patients with congestive heart failure (NYHA Class IV) and the finding arose from post hoc sub-group analysis[99]. A trial with metoprolol in 383 patients with dilated cardiomyopathy did not achieve a statistically significant reduction in deaths in the active treatment group compared to those on placebo[102]. Zamoterol in 516 patients with congestive heart failure of mixed aetiology was associated with a significant increase in mortality[103]. More recently, the SWORC trial with d-sotalol in 3000 patients with post-infarction left ventricular dysfunction was discontinued because an interim analysis revealed a 3.9% death-rate on the beta-blocker compared to 2.0% in the placebo group. These discouraging results must caution against speed acceptance of beat-blocking drugs as a conventional addition to currently available agents, particularly as they have little clinically discernible impact on symptoms. For these reasons it is imperative that the effect of these drugs, both on quality of life and on the high mortality risk of patients with congestive heart failure, be clearly determined as the next step to their recommendation for routine clinical practice.

From the practical viewpoint, a number of important clinical considerations arise. The first relates to the functional disability of the patients to whom these drugs may be administered. In the majority of studies reported, the patients have been those with mild or moderate symptomatic disability, namely New York Heart Association Classification II or III. This is a crucial consideration as the administration of beta-blocking drugs, even in very small doses, to patients with severe heart failure (NYHA Class IV) has been shown to result in further depression of cardiac dysfunction[104,105]. For this reason, the clinical results of beta-blockade may differ widely between patients with different degrees of functional disability; possible benefit in patients with milder degrees of heart failure cannot be translated into similar benefits in more severely ill patients. None of the reported trials have included elderly patients. As the incidence of heart failure is age-dependent and as the elderly are more sensitive to the cardiovascular consequences of beta-blockade, this glaring pharmacotherapeutic omission awaits clarification. With regards to the aetiology of the heart failure, it is important to emphasize that the majority of the studies so far reported with a range of beta-blocking drugs have predominantly been concerned with their efficacy in patients with idiopathic dilated cardiomyopathy[96–98]. Such patients comprise the minority of those presenting with heart failure in clinical practice. A further point of practical clinical importance relates to concomitant treatment. In all the clinical trials so far reported, beta-blocking drugs have only been administered to patients already pre-treated with diuretics, digitalis and often a vasodilator; they have never been given as first-line treatment. The starting dose of beta-blocking drug and dose titration also requires particular attention. It would appear from published studies that the clinical efficacy of beta-blockade in patients with symptomatic heart failure is best achieved when these are introduced in a low dose and only gradually titrated under close clinical monitoring. Unfortunately, there is no ready clinical test with which to monitor such progress. The primary reason for the administration of beta-blocking drugs in the treatment of heart failure is to reduce morbidity and extend life-span; in the trials so far reported, beta-blockade has had no substantial effect on symptoms.

Considerable debate has concerned the efficacy stature of different beta-blocking drugs in the treatment of severe heart failure, but with the paucity of data currently available it is a question still without a definite answer. The first generation of these drugs, the archetype of which was propranolol, caused profound depression of cardiac pumping, not only due to their negative inotropic activity but also due to the reflexly increased peripheral vascular resistance and aortic impedance which further depressed cardiac function. The second generation of these drugs, archetypes of which are atenolol and metoprolol, are relatively beta-I selective but in the doses used in clinical practice this selectivity is frequently eroded to the point of extinction. The latest generation are those which possess peripheral vasodilating activities in addition to their prime function of beta-adrenoceptor blockade. The vasodilatation is designed to offset the increase on systemic vascular resistance and further depression of cardiac function. In this regard, therefore, it is reasonable to argue that this third generation of beta-adrenoceptor antagonists, namely those with ancillary vasodilating activity, may well turn out to be the beta-blocking drugs of choice should this category of drug eventually be accepted as an adjunct to other conventional treatments of heart failure.

At the present time many outstanding questions of practical importance remain to be answered before these drugs can be safely recommended for general use in the treatment of congestive heart failure. Not least amongst these questions are the age of the patient to be treated, the aetiology of the heart failure, the degree of functional disability and the adequacy of concomitant anti-failure treatment. Hopefully, the extensive clinical
research programmes and large-scale survival trials now underway with a variety of beta-blocking drugs will furnish sufficient positive evidence for them to be accepted as yet another important pharmacotherapeutic step towards the goal of a comprehensive treatment of the patient with congestive heart failure.

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