Clinical trials in heart failure (HF) tend to randomize patients according to demographic characteristics and severity of left ventricular dysfunction, without taking account of the precise diagnosis. This article reviews results from recent trials suggesting that the etiology of HF, and particularly whether it is ischemic or nonischemic, may influence the long-term prognosis and the response to treatment. Some studies, but not all, suggest that nonischemic HF has a better prognosis than ischemic HF. The data on the benefits of angiotensin-converting enzyme inhibitors in ischemic versus nonischemic HF are conflicting. Carvedilol, and recently, bisoprolol have been shown to reduce mortality in ischemic and non-ischemic HF, whereas metoprolol has, to date, improved prognosis only in dilated cardiomyopathy. Better responses to digoxin, amlodipine and amiodarone have been reported in non-ischemic HF. There is at present no clear explanation for the apparent therapeutic differences between ischemic and nonischemic HF. Absence of a rigorous definition of “nonischemic HF” in many studies makes interpretation of the results difficult. Further studies to clarify the effects of etiology of HF on the response to treatment could be particularly important for preventing progression to more advanced stages, in which any type of drug therapy may have limited value in prolonging survival. An individualized therapeutic approach, based on etiology of HF and possibly other factors such as plasma drug levels or the levels of neurohormones, could result in major progress in treating HF patients.

In large-scale therapeutic trials in heart failure (HF), patients are usually randomized according to demographic characteristics and the severity of left ventricular (LV) dysfunction. Many specialists share the view expressed by Franciosa (1) that “there is little reason to know the precise diagnosis, since the treatment of heart failure is essentially the same in most of these situations.” However, recent trials suggest that the cause of HF may influence the long-term prognosis and the response to certain pharmacologic treatments. This review discusses the extent to which the etiology of HF—particularly ischemic versus nonischemic HF—influences the prognosis and the response to drug treatment.

**Epidemiology of Heart Failure**

Population studies indicate that about 1% to 2% of the population have HF and that it is predominantly a disease of the elderly (2,3). A population-based study in the United States reported that the prevalence of idiopathic dilated cardiomyopathy and hypertrophic cardiomyopathy combined was 36.5 per 100,000 (4). This suggests that cardiomyopathy accounts for about 2% of cases of HF. The proportion of patients with a diagnosis of cardiomyopathy in clinical trials is much higher, ranging from 18% (5) to 53% (6).

**Pathophysiology of Ischemic and Nonischemic HF**

In ischemic heart disease (IHD) three processes can occur:

- myocardial infarction (MI), which destroys a discrete mass of myocytes,
- chronic myocardial dysfunction, which includes hibernation and stunning and, possibly, progression to diffuse cardiac myocyte death
- myocardial dysfunction as a result of acute, reversible ischemia.

In most patients with dilated cardiomyopathy (DCM), the cause of the condition is unknown or uncertain (7). Over 20% of patients have familial disease (8). This does not appear to be clinically distinguishable from the nonfamilial form. There is evidence that at least some patients with DCM express anti-myosin antibodies (9) and others express beta-receptor antibodies, some of which may be physiologically active and possess beta-agonist function (10–12). Compared with control subjects or patients with ischemic HF, patients with DCM have significantly greater levels of immunoreactive staining to the inducible form of nitric oxide synthase (iNOS) in cardiac myocytes, and to tumour necrosis factor alpha (TNFα) in
vascular endothelium and smooth muscle cells (13). In patients with DCM, an inflammatory reaction (triggered by an autoimmune or infectious event) could stimulate production of TNFα, leading to induction of iNOS and elevation of the levels of NO, which has a negative inotropic effect on cardiac myocytes (14), and, at high concentrations, has cytotoxic effects, probably through generation of free radicals (15).

In both ischemic and nonischemic HF, chronic activation of neuroendocrine systems has harmful effects on cardiac structure and function (16–18). Oxidative stress, involving the formation of oxygen free radicals, may play a critical role in the pathogenesis of HF, even in the absence of coronary artery disease (CAD) or ischemia (19–21).

**Differential Diagnosis of Ischemic Versus Nonischemic HF**

In many patients, the combination of signs and symptoms of HF with a history of angina pectoris or MI is sufficient to support a diagnosis of ischemic HF, whereas in the absence of significant epicardial coronary artery obstruction or an obvious cause of HF, a diagnosis of DCM is made. An apparently normal coronary angiogram does not rule out myocardial ischemia because several other processes, including coronary artery spasm, compression of subendocardial coronary vessels, a reduction in the coronary vasodilator reserve and the presence of hypertension and a high heart rate, can produce ischemia in the absence of detectable coronary artery obstruction (22–24).

Imaging studies can be used to assess the degree of LV dilatation and dysfunction. Prominent localized wall motion disorders are more characteristic of IHD, whereas diffuse global dysfunction is more typical of DCM (25). The roles of thallium-201 imaging and positron emission tomography for distinguishing DCM from ischemic HF are under investigation (26–29).

If DCM is suspected, basic biochemical screening tests to identify potentially reversible causes (e.g., hypocalcemia, thyrotoxicosis, hypophosphatemia) are indicated (28).

**Prognostic Differences Between Ischemic and Nonischemic HF**

A number of studies have shown that DCM has a better response to treatment and a better prognosis than HF resulting from IHD (30–34). Several large mortality trials in HF (35–37) also reported that within the placebo arm, mortality was lower in patients with nonischemic HF than in those with ischemic HF, although other studies have reported similar mortality in these subgroups (38–40) (Table 1). Clinical trial reports, however, rarely explain fully how the etiology of HF was diagnosed, and many case report forms are inadequate in this respect. In these trials, therefore, the etiology of HF is not known with certainty. Explanations of the apparent differences between ischemic and nonischemic HF are therefore tentative.

The worse outcome and poorer response to treatment in ischemic than nonischemic HF in some clinical trials may have been an effect of patient selection. For example, patients with IHD suitable for revascularization, who have regions of viable myocardium that can respond to treatment, were excluded from some trials. Alternatively, the better prognosis of nonischemic HF may reflect the absence of CAD or recurrent MI, or the lower average age of patients with DCM. For example, in the Metoprolol in Dilated Cardiomyopathy (MDC) Trial, the mean age of patients was 49 years (41) and in a recent series, mean age was 43 years (42).

Data from clinical trials are in marked contrast to community data from Framingham, which suggest that, if anything, men who develop HF as a result of CAD do better than those with other etiologies of HF (43).

**Pharmacologic Treatment of Ischemic Versus Nonischemic HF: Evidence From Clinical Trials**

**Diuretics.** There is no information on the effects of diuretics on morbidity or mortality in ischemic versus nonischemic HF. It is very difficult to obtain such information because the dose of diuretics is frequently adjusted to maintain optimum fluid balance, and it is not justifiable to withhold these drugs from patients with fluid retention for the purposes of a clinical study.

**Cardiac glycosides.** Pooled results from the PROVED and RADIANCE trials indicate that digoxin increases LV ejection fraction more in patients with DCM than in patients with IHD, and that withdrawal of digoxin leads to significantly greater likelihood of clinical deterioration in the DCM patients (44,45). In the Digitalis Investigators’ Group trial (46), digoxin was associated with a significant reduction in a combined end point of death or hospitalization as a result of worsening HF in patients in sinus rhythm. This benefit was somewhat greater in patients with nonischemic etiology than in those with ischemic etiology (46). There is no evidence that the effect of digoxin on survival differs between ischemic and nonischemic HF.
Effects of Beta-Blockade

Clinical trials have shown that beta-blockers, primarily carvedilol, metoprolol and bucindolol, improve hemodynamics, LV function and clinical status in patients with HF of ischemic or nonischemic etiology (49). These studies led to large, long-term trials to evaluate the effects of beta-blockade on morbidity or mortality in HF. The MDC trial enrolled only patients with DCM, mainly New York Heart Association (NYHA) class II or class III (41). The definition of DCM was not described in detail, but patients with >50% obstruction of a major epicardial coronary vessel, or clinical or histologic signs of ongoing myocarditis, were excluded. Metoprolol had no significant effect on all-cause mortality, but was associated with a borderline significant reduction in a combined end point of death or the need for heart transplantation and significant reductions in the need for heart transplantation and in the number of hospitalizations per patient.

The Cardiac Insufficiency Bisoprolol Study (CIBIS) investigated the effects of bisoprolol on morbidity and mortality in patients with HF of NYHA class III or class IV (38). The most common cause of HF was ischemia (about 55% of patients), but patients with idiopathic DCM (about 35% of patients), hypertension (about 5% of patients) and valvular heart disease (about 5% of patients) were included. After a mean 1.9 years of follow-up, survival was improved on bisoprolol therapy, compared with placebo, only in the subgroups without a history of MI or in those with DCM as the sole diagnosis, but not in those with a history of MI. The mortality in the placebo arm was about 20% in all of these subgroups. The failure to reduce mortality in the ischemic subgroup may have reflected the exclusion of patients suitable for revascularization who might have had a greater potential to respond to the anti-ischemic effects of beta-blockade than patients unsuitable for surgical treatment.

CIBIS II was a much larger placebo-controlled trial of bisoprolol in severe (NYHA III/IV) HF (50). The main results were presented at a recent Congress of the European Society of Cardiology (50a). There was a significant 32% reduction in all cause mortality regardless of the etiology of HF.

A program of placebo-controlled trials has investigated the effects of carvedilol on morbidity and mortality in patients with HF resulting from CAD or nonischemic DCM (39,51–54). Over a median follow-up of 6.5 months, overall mortality was reduced by 65% in patients receiving carvedilol, compared with the placebo group, and this benefit was virtually identical in patients with ischemic or nonischemic etiology. The low overall mortality in this trial (<10% on placebo and <5% on carvedilol, regardless of etiology) makes it difficult to detect differences in mortality between patient subgroups. Carvedilol has potent antioxidant activity (55), which may have contributed to the reduction in mortality observed in this program by preventing cardiac myocyte dysfunction, necrosis or apoptosis.

The Australia–New Zealand HF study enrolled patients with HF solely due to IHD (56,57). In this trial, carvedilol was associated with a nonsignificant trend towards lower mortality and a reduction in a combined end point of death or all-cause hospitalization after a mean follow-up of 19 months, compared with the placebo group. The absence of a significant effect on mortality in this trial may have been a result of its small size and the very mild HF and low mortality of the patients enrolled.

Comparative trials between beta-blockers in HF are required to clarify whether the differences in outcome seen in the studies summarized above result from patient selection or the properties of the agents. The first such study is COMET (Carvedilol or Metoprolol European Trial), which started in November 1996 and is due to end in August 2000 (58). This is a randomized double-blind trial of carvedilol (starting dose 3.125 mg b.i.d. titrated to 25 mg b.i.d.) versus metoprolol (starting dose 5 mg b.i.d. titrated to 50 mg b.i.d.) in 3,000 patients with NYHA class II to III HF, despite conventional therapy. Patients with HF of ischemic and nonischemic etiology will be included. The primary end point will be all-cause mortality. Secondary end points will include cardiovascular deaths and changes in NYHA class.

Amiodarone. Two randomized trials of amiodarone have been performed in HF. GESICA examined low-dose (300 mg/day) amiodarone in severe HF (59). Overall mortality and hospital admission for worsening HF were significantly lower in the amiodarone group than the control group in all patient subgroups examined. In the larger CHF-STAT trial, amiodarone did not significantly reduce the incidence of sudden death or prolong survival, but there was a trend toward reduced mortality among patients with nonischemic cardiomyopathy (60,61).

Calcium Antagonists. Studies of calcium antagonists conducted before the use of ACE inhibitors became widespread indicated that diltiazem (62) and nifedipine (63) could adversely affect the prognosis of HF. More recent results with diltiazem (64) and felodipine (65,66), in contrast, suggest no effect on overall mortality (65). The PRAISE trial (40) showed that among patients with nonischemic HF, amldopine reduced the risk of fatal and nonfatal cardiac events by 31% (p < 0.04) and decreased the risk of death by 46% (p < 0.001), but there was no effect on either of these end points in the group with IHD. However, in this trial the definition of “nonischemic dilated cardiomyopathy” was not rigorous, and patients with undetected CAD may have been included in this group (67). A
second trial with much more stringent criteria is being conducted to test the validity of the results observed in patients without IHD.

Conclusions

Since the introduction of ACE inhibitors, the improvement of prognosis has become an important objective in the management of HF. There is some evidence that the etiology of HF influences its response to beta-blockers and possibly ACE inhibitors and calcium antagonists. The response to other treatments with a potential benefit on prognosis (e.g., angiotensin II receptor antagonists) might also be dependent on etiology. Identification of the etiology of HF might become more important as physicians aim to select the optimum treatment from the increasing number of options available. At present, however, the incomplete documentation of the cause of HF in many studies, the conflicting results in the literature and the presence of confounding factors (e.g., the young mean age of the patients in many trials of DCM) mean that recommendations for the treatment of HF based on etiology are tentative. Moreover, the lack of interest in establishing etiology could contribute to frequent undertreatment of HF.

The conflicting reports on the benefits of ACE inhibitors in ischemic versus nonischemic HF make it impossible to provide firm recommendations on the use of these agents based on etiology. Most of the evidence for the benefits of ACE inhibition comes from patients with IHD, and the reduction of reinfarction by ACE inhibitors applies only to this group. A study of ACE inhibitors in clearly defined DCM would be valuable.

Carvedilol and now also bisoprolol have been shown to reduce mortality in both ischemic and non-ischemic HF, whereas metoprolol has, at present, improved prognosis only in patients with dilated cardiomyopathy. However, none of the beta-blocker studies have been designed to compare long-term outcome in HF of different causes. To answer this question and to evaluate possible differences between various types of beta-blockers requires further trials such as COMET.

The results obtained in the nonischemic subgroup of the PRAISE trial are the only report of a reduction in mortality in HF by a calcium antagonist. Patients with hypertensive HF might benefit from calcium antagonists via a reduction in blood pressure, but this suggestion has not been tested in a randomized controlled trial.

The selection of the initial drug therapy based on etiology could be of particular importance at the early (NYHA class I to II) stages of HF. Identification of pathogenic factors, such as immunologic processes, inflammation with cytokine activation, neurohormone levels and abnormalities of serum lipids, fibrinogen and thrombophilic factors would allow a more selective, targeted intervention with appropriate drugs. If an ischemic etiology is established, preventive therapy with lipid-lowering agents and in future antibiotics to eliminate *Chlamydia* (68) could be as important in preventing further progression of HF as the anti-HF drugs used today. On the other hand, growth hormone or insulinlike growth factor may be an appropriate treatment in patients with cardiomyopathy (69). Whether beta-blockers or ACE inhibitors will have an advantage as the first intervention remains to be studied, since most patients received ACE inhibition as part of their background therapy in the beta-blocker trials. Controlled comparative trials such as CARMEN (Carvedilol ACE inhibitor Remodelling Mild HF Evaluation), which will evaluate carvedilol versus enalapril versus carvedilol + enalapril in 450 patients with mild HF (70), are therefore of considerable practical interest.

As more therapeutic options are developed, individualized drug selection for patients with HF might become possible. Furthermore, individually adapted rather than schematic dosage regimens based on clinical (heart rate, heart rate variability, blood pressure) and laboratory (natriuretic peptides, cytokines, drug level measurements) criteria could contribute to improved efficacy and better long-term tolerance of drugs in HF. An early and precise diagnosis of the etiology of heart failure should be encouraged not only in future clinical trials but also in everyday patient management.

References


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