Hotline Editorial

Slowing the progression of heart failure

Publication of the results of the U.S. carvedilol programme\(^1\) has created an international dilemma affecting patients, physicians and drug regulatory agencies. The data presented in the New England Journal of Medicine of 23 May 1996 were from the overall study population of 1094 patients with symptoms of chronic heart failure, a left ventricular ejection fraction \(\leq 0.35\), and the ability to perform a corridor walk test. All were on what was viewed as optimal therapy with diuretics and a converting enzyme inhibitor. They were randomly assigned to treatment with carvedilol or placebo. During an average of 6 months of follow-up 7.8% of the placebo group but only 3.2% of the carvedilol group died, a 65% mortality reduction with 95% confidence intervals from 39 to 80%. This statistically remarkable benefit was also reflected in a 27% reduction in the need for hospitalization for cardiovascular causes.

Carvedilol is a non-selective \(\beta\)-adrenoceptor blocker that exerts a vasodilator effect through \(\alpha\)-receptor blockade and has also been shown to have potent antioxidant properties. Should the drug-induced reduction in short-term mortality in this population of patients with mild to moderate symptomatic heart failure be taken as evidence that \(\beta\)-blockers prolong life? Do these data suggest that all patients with heart failure should be treated with carvedilol if tolerated? Is there adequate evidence of efficacy and safety to justify approval of this drug for treatment of heart failure?

The complexity of these questions relates not only to one's interpretation of the data from the carvedilol studies but also to our emerging understanding of heart failure. The syndrome appears to involve two largely independent processes: (1) dysfunction and remodelling (dilatation) of the left ventricle, and (2) a symptom complex characterized by congestion and exertional fatigue. Treatments for heart failure have traditionally been evaluated on the basis of their efficacy in short-term symptom relief, for which exercise testing and, more recently, quality of life questionnaires have been used as guides. However, an equally important and perhaps more modifiable goal would be slowing of progression of the syndrome. These anatomical and physiological changes may well be accompanied by long-term effects on symptoms and the need for hospitalization, but early drug-induced changes in exercise tolerance and quality of life, indicative of a therapeutic effect on symptoms, is quite distinct from a therapeutic effect to delay or prevent the worsening of the syndrome over time.

The dissociation between symptoms and left ventricular structure was probably best exemplified in the SOLVD Prevention Trial which sought asymptomatic individuals with dilated, dysfunctional left ventricles (ejection fraction \(\leq 35\%\)) for randomization to enalapril or placebo therapy\(^2\). Over 4000 patients were recruited into this trial, and their ejection fractions (mean 0.28) largely overlapped with those in the SOLVD Treatment Trial with symptomatic heart failure (mean 0.25). The success of enalapril in reducing the rate of development of symptomatic heart failure in the Prevention Trial was taken as evidence that converting enzyme (ACE) inhibitor therapy should be used to prevent congestive heart failure. More significantly, however, ACE inhibitors in the SOLVD\(^3\) and post-myocardial infarction SAVE Trials\(^4\) delayed the progressive structural and/or functional abnormality in the left ventricle by resulting in a higher ejection fraction in the treated than in the placebo groups. Even in the absence of an early symptomatic benefit, this physiological effect might be expected to result in a long-term reduction in morbidity events and mortality.

In dealing with a therapy for heart failure, therefore, we should define whether our goal is short-term relief of symptoms or long-term slowing of the rate of progression of the disease.

Therapeutic use of \(\beta\)-blockers for heart failure has had a long and controversial history. Early trials with metoprolol in Sweden were uncontrolled observational studies that suggested a long-term benefit on morbidity and mortality\(^5\). Even in these early trials it was emphasized that symptoms often worsened in the early weeks or months after initiating the gradually titrated regimen. The failure of subsequent short-term placebo-controlled studies to demonstrate symptom relief was the expected outcome with a drug aimed at slowing progression rather than at short-term improvement in exercise tolerance. However, the rather unimpressive and unpersuasive
long-term morbidity and mortality benefit of $\beta$-blockers in more recent larger-scale studies tended to temper the enthusiasm of those who were optimistic that this therapy could strikingly alter the natural history of the disease$^{[6,7]}$.

During the years intervening between the first reports of $\beta$-blocker efficacy and the design of the carvedilol studies, considerable change has taken place in the management of heart failure. ACE inhibitors have become mandated therapy because of their efficacy in reducing mortality and their physiological rationale to inhibit diuretic-induced renin-angiotensin–aldosterone stimulation that contributes to unwanted vasoconstriction and potassium loss. However, symptom relief has been an elusive and inconsistent result from ACE inhibitor therapy, and the modest magnitude of the mortality reduction leaves treated patients with a persistently poor prognosis. In addition, short-term symptom relief has been demonstrated to be independent of long-term outcome; several drugs appear to exert favourable haemodynamic, symptom and exercise effects while shortening life expectancy$^{[8-10]}$. All of these trial data have left us with a standard drug regimen, but the clear need for additional pharmacotherapy to improve quality of life and life expectancy.

The statistically significant mortality reduction observed in the carvedilol-treated patients in the recently reported 6-month trials has generated controversy because of the low overall event rate and the unusual trial design. This was not a traditional mortality study with a uniform randomization schema but rather a series of smaller studies each with a slightly different treatment regimen and different primary end-points. The entire study programme was terminated early by the independent Data Safety and Monitoring Board, but their reasons were heterogeneous. Some felt the mortality data were so persuasive that continuing placebo therapy was unethical. Others attribute their decision to recognition that the 6-month trial design could not more conclusively demonstrate a mortality reduction. These members thought they were terminating the trial so that a more definitive long-term mortality trial could be designed.

The Food and Drug Administration Cardiorenal Advisory Committee raised an additional issue. Is it appropriate for these studies to even evaluate a mortality benefit of carvedilol, since the primary symptom and exercise end-point, on which the individual trials were powered, was not uniformly met? This somewhat arcane debate should not dissuade us from looking at the data, which reveal a remarkably consistent carvedilol-related reduction in mortality and hospitalization across all studies. Given the imaging data in this and previous trials of a striking $\beta$-blocker induced regression of the structural and/or functional abnormality of the left ventricle, it is unlikely that these morbidity and mortality effects were chance observations.

Then what have these studies shown? The Cardiorenal Committee voted — before they recommended rejection of the request by the sponsor for approval of the drug — that if the drug was effective its benefit was to 'prevent progression of heart failure'. This was both an insightful and naive decision. It was insightful because it displayed recognition that heart failure is a progressive process and that short-term relief of symptoms or improvement in exercise capacity is a quite different therapeutic goal than prevention of the progressive process leading to recurrent hospitalizations, worsening quality of life and shortened life expectancy. It was naive, however, because the agency has yet to deal with how to define progression and, therefore, what effects can be accepted as a guide to delay in this progression. Nonetheless, the committee was in a bind because the small number of events led some to demand replication and the unusual design made it statistically improper to accept the mortality data as pivotal. There was no single end-point other than the nebulous 'progression'.

What may emerge from this contentious debate, however, is a new paradigm for the treatment of heart failure and potentially new targets for assessment of efficacy.

Do we now have an adequate data base to approve carvedilol and use it routinely for delaying progression of heart failure? Many experts feel that they do — and these sophisticated physicians are ready to use the drug with care and intelligent monitoring. It is likely that at least a subset of patients offered this therapy will experience long-term benefit. But the concept of 'slowing progression' without short-term symptom relief is a difficult therapeutic strategy for the average physician to apply. Slow drug titration is also anathema to many primary care physicians who may share their patients' frustration that this new and expensive drug is not making them feel better. Thus I suspect we will need more extensive data and more insight into subgroup responsiveness before this exciting pharmacotherapy can penetrate usual clinical practice.

Finally, do the results of these trials provide the long-sought evidence that $\beta$-blocker therapy is beneficial for heart failure, or should the apparent effect of carvedilol be attributed, at least in part, to its other pharmacological effects? It is certainly too early to ascribe the early carvedilol data to a class action of $\beta$-blockers. A trial comparing carvedilol to metoprolol is currently in planning. A large scale trial of
another β-blocker with vasodilating effects, bucindolol, is currently ongoing in the United States (BEST).

As always, we need more data in larger numbers of patients with different aetiologies of heart failure and a wider range of severities followed for longer periods of time to place carvedilol or other β-blockers in the proper therapeutic position in the multiple drug regimen currently employed in heart failure. How the various drug regulatory agencies deal with this dilemma during this phase of an incomplete database will undoubtedly be influenced by regional social, philosophical, political and health care system issues.

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References


