

## **Beta-adrenergic receptor blocking therapy for congestive heart failure: an overview**

*J.C. Mohan\**

It is uncommon for clinical trials to be prematurely terminated because of formidable evidence in favour of a particular agent or strategy and rare for such trials to be reported in lay press. This is what has precisely happened with regard to beta-adrenoceptor blocking therapy in patients with congestive heart failure twice once in 1996 and again in March, 2000. The drug in question has been carvedilol (a beta-adrenergic receptor blocking agent) and the trials were Carvedilol US Heart Failure Study and GOPERNICUS (Carvedilol Prospective Randomised Cumulative Outcome Study). The therapy in patients of congestive heart failure has shown a remarkable change over a period of last three decades ever since it was shown by a Swedish team that in some patients with heart failure, beta-blocking agents can cause symptomatic improvement in refractory heart failure. The current theme is no longer symptomatic relief which is variable but survival benefits and less need for cardiac transplantation and recurrent hospitalization. Saga of beta-blocker therapy taught us how mechanistic approach and experimental data do not always provide the correct answer to a complex pathophysiological syndrome. Besides, there have been some lessons about the appropriate adequacy of power of randomized controlled trials and the dose and the type of the agents used. Had researchers not pursued the work in this direction after initial not too encouraging results, we would not reach this stage wherein there is consensus on the use of beta-blockers in patients with stable congestive heart failure. The therapy is no longer confined to refractory heart failure, tachycardiomyopathy, high output failure or a freak case with undue sinus tachycardia .

Heart failure which was initially thought to be a cardiorenal problem in early forties and then a condition with inefficient pump in early 1960-70, has now come to be recognized mainly a neuroendocrine syndrome with initiating events residing in heart. Activation of sympathetic nervous system, deactivation of parasympathetic system, enhanced plasma and tissue activity of renin- angiotensin-aldosterone axis and interplay of several other local endocrine compounds like natriuretic peptides, endothelins, bradykinin etc has been shown in patients with heart failure. Cardiotoxicity of catecholamines (hypertrophy , excessive growth, hypokalemia, apoptosis, free radical generation) and down regulation of beta-adrenergic and other receptors has been well recognized. Obviously with this knowledge and also with the increase in beta-receptor density in experimental heart

failure with beta-blocking agents, it was only natural to expect large trials on the subject. Year 1999 was a watershed year when two large trials (GIBIS-II and MERIT-HF) using beta-adrenergic blocking drugs in heart failure changed our perception completely. The possible mechanisms of benefit are improved myocardial energy kinetics, improved systolic function due to up regulation of beta-receptors, anti-arrhythmic effects, anti-ischemic effects, change in diastolic behaviour and coronary blood flow and additional properties of some of the beta-adrenergic blocking compounds (anti-proliferative and anti-oxidant effect). It is yet to be known if the all benefits are a class effect or there is some agent-specific activity as well. To some extent, all beta-blocking agents have antiplatelet, anti-inflammatory and antioxidant features. Trials on secondary prophylaxis of myocardial infarction taught us that beta-blockers were more beneficial in patients with high risk like left ventricular dysfunction, anterior wall myocardial infarction, significant ventricular ectopy and those who did not receive thrombolysis. Similar conditions prevail in a large majority of patients with heart failure.

Heart Failure is a complex heterogeneous syndrome and looking at simple numbers with regard to decrease in total or cardiovascular mortality in a trial may be fraught with errors. Whether to use metoprolol (MERIT-HF) or bisoprolol (CIBIS-II) or carvedilol to individual choice as the quantum of benefit shown with each compound can not be compared with certainty. COMET which is a trial comparing metoprolol and carvedilol may give some answers. There is also the issue of commercial hype with non-scientific motives. Statistical improvement and clinical benefits are not synonymous and in a relentless disease like heart failure living a little longer with similar symptoms (which is what beta-blockers promise to deliver) may not always be welcome. But then do not the other agents like angiotensin-converting enzyme inhibitors and statins do the same. If quality of life is more important, beta-adrenergic blocking agents with so many trials and megabucks spent, are not what a dying man is looking for. However, the Society and the Health care providers think the other way since recurrent hospitalization and cardiac transplantation are expensive while death has a one time cost and the symptoms only concern the patient and his/her immediate family. Nevertheless, beta-blocking therapy is definitely more effective than angiotensin-converting enzyme inhibitors, antiarrhythmic drugs and aldosterone antagonists which all have been shown to be useful in patients with heart failure.

First serious attempt to test use of beta-blocking agents in heart failure was in MDC trial. In 383 patients with congestive heart failure, long term treatment with metoprolol (up to 100 mg/day) found a 34% decrease in death and need for cardiac transplantation ( $p=0.058$ ) in actively treated patients.

CIBIS-I study also showed a non-significant 20% reduction in total mortality and 30% reduction in hospitalization in patients with heart failure due to a variety of causes on treatment with bisoprolol, a selective beta-1 receptor antagonist. First real breakthrough in this direction came in 1996 with publication of Carvedilol US Heart Failure Trial involving 1096 patients followed up at four centers. Although not the primary end point of the study, a 65% reduction in mortality was too dramatic to be ignored. A similar design of study using carvedilol in New Zealand-Australian Trial (1997) found modest benefits with carvedilol with a 26% reduction in mortality + hospitalization without and symptomatic benefits. Publication of large adequately powered CIBIS-II (n=2647, bisoprolol) and MERIT-HF (n=3991, metoprolol up to 200 mg/day) trials in 1999 have compelled physicians to include beta-blocking therapy as a standard regimen in patients with heart failure as has been suggested in a consensus statement by the Action Heart Failure Group led by Jay Cohn in January, 1999. Both these trials have shown a substantial reduction in all cause mortality (34%) along with significant reduction in sudden cardiac death, cardiovascular events and recurrent hospitalization .

There are of course a large number of practical points to be considered. Titrating dose has to be 5% of the standard dose with gradual increase during hospitalization which is a time consuming and expensive procedure. Overall 5-15% may not tolerate beta-blockers and the number is larger in sicker and class IV patients. At the moment, it appears that beta-blocking drugs are suitable for systolic dysfunction with heart failure in stable class II-III patients. There is limited data on unstable patients and class IV patients, although CIBIS-II and MERIT-HF did include <10% class IV patients. These agents can not be used as a rescue therapy because there are no consistent symptomatic benefits and effects are seen only on long-term treatment. Patients with sinus tachycardia are likely to respond better and those with diabetic or alcoholic heart failure are least likely to respond. Therapy to show benefit must be given for several months. The information with non-selective beta-blockers is limited. We do not have information about differential benefits in heart failure of ischemic vs non-ischemic etiology. The issue of diastolic versus systolic heart failure needs attention. It is unlikely that every patient will respond equally to this therapy.

In conclusion, benefit of beta-blocking drug therapy in patients with stable mild to moderate heart failure is certain and substantial and should be included in modern practice guidelines.

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\* *Professor of Cardiovascular Sciences*  
*G.B. Pant Hospital, New Delhi, India*