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Beta-Blockers in Severe Heart Failure

S. Goldstein

Beta-blockers have been demonstrated to have a significant benefit in the treatment of heart failure. Nevertheless there is a reluctance to use these agents because of their potential adverse effects in patients with severe heart failure. Analysis of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial, and the sub-group analysis of the Metoprolol CR/XL Randomized Intervention Trial in Chronic Heart Failure (MERIT-HF) in patients with severe heart failure, in NYHA Class III/IV with left ventricular ejection fraction < 25 % showed a significant survival benefit. In addition the frequency of withdrawal for any reason and for increase in heart failure symptoms were less frequent than in the placebo group. These observations indicate that beta-blockers are safe and effective when administered to patients with severe heart failure who are stable on angiotensin converting enzyme inhibitors. *J Clin Basic Cardiol 2002; 5: 155–8.*

Key words: beta-blocker, heart failure

The remarkable changes that have occurred in the treatment of heart failure in the last decade culminated in the demonstration in three randomized mortality trials [1–4], that beta-adrenergic blocking agents (BB) have a profound effect on decreasing mortality and morbidity in patients with left ventricular dysfunction. The development of angiotensin converting enzyme inhibitors (ACEI) represented the first major advance in the treatment of heart failure since Withering described the effects of digitalis almost three centuries ago. Although ACEI agents have significant vasodilator effects, their autocrine and paracrine action on the cardiomyocyte in heart failure are both more complex and relevant to their clinical benefit. It is now clear that among the effects of ACEI on the cardiomyocyte are their ability to modify the stimulus of the cell to hypertrophy and for the fibroblast to lay down interstitial collagen in the setting of increased myocardial wall stretch. The beneficial effects of ACEI in heart failure stimulated the investigation of the Renin Angiotensin System (RAS) and the Sympathetic Nervous System (SNS). As a result, the importance of the SNS and its principal messenger, norepinephrine became the focus of attention. The subsequent demonstration that BB decrease mortality in heart failure represented a major paradigm shift in cardiovascular therapeutics. In spite of these important observations, there remains a reluctance to use BB because of their potential adverse effects in patients with advanced and more severe heart failure.

The pathophysiology of heart failure is complex and varies relative to the duration and severity of the disease. In the setting of heart failure, the heart and its constituent cardiomyocytes are functioning at a severe disadvantage as a result of increase in heart rate, hypoxia and an increase in peripheral vascular resistance. In acute left ventricular decompensation, activation of the RAS and the SNS are important for the maintenance of haemodynamic homeostasis. However, in chronic heart failure, activation of the RAS and SNS can now cause progressive ventricular dysfunction. Activation of the two systems leads to increase in blood and tissue concentration of both angiotensin II and norepinephrine [5]. These hormones can lead to progressive decrease in ventricular function and an increase in cardiac symptomatology. The increase in plasma norepinephrine poses an additional toxic effect on the cardiomyocyte [6] and is directly related to cardiac mortality [7]. In addition, activation of the SNS leads to electrical dysfunction of the cardiomyocyte creating an environment prone to the development of life threatening arrhythmias [8]. The clinical manifestations of these events lead to worsening of symptoms often associated with cardiac arrhythmias.

In patients with severe heart failure the cardiovascular system is in a very tenuous balance. On one hand, depending upon the increase in circulating catecholamines to maintain homeostasis and at the same time adversely effected by the cardiotoxic and hypermetabolic effects of these hormones. In patients with advanced severe heart failure in the setting of a decrease in cardiac output, the increase in circulating norepinephrine may be all that is maintaining haemodynamic stability. At the same time the constituent cardiomyocytes have become desensitized to the effect of norepinephrine due to the down regulation of the beta-receptors [9]. Because of this fragile physiologic environment, the benefit and safety of BB therapy in patients with severe heart failure can be uncertain. It is therefore both remarkable and paradoxical that the introduction of BB can lead to improvement of both ventricular function and symptomatology of heart failure not only in patients with mild to moderate heart failure, but also in patients with severe and advanced heart failure [1–4].

The Metoprolol CR/XL Randomized Intervention Trial in Chronic Heart Failure (MERIT-HF) [1, 2] has within its study population patients with severe heart failure [16]. The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) [4] study specifically investigated this more severe heart failure population. This review will discuss the effect of BB on cardiac function in severe heart failure and discuss the findings of these two randomized mortality trials and their implications.

Haemodynamic Effects of Beta-Blockers in Heart Failure

It has been known since 1975 as a result of the pioneering work of Waagstein that BB and specifically metoprolol can improve ventricular function and symptomatology of heart failure patients [10]. This improvement is associated with a decrease in left ventricular filling pressures (PCWP) and an increase in left ventricular ejection fraction (LVEF), stroke volume index without increasing myocardial oxygen consumption. A number of studies confirmed the benefit of a variety BB on

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cardiac function in symptomatic patients with LVEF < 30 %. Studies with carvedilol in patients with mean LVEF of 16 % showed significant haemodynamic improvement and an increase in LVEF to 24 % after 14 weeks of therapy [11]. The improvement in LVEF associated with BB therapy, an example of "reverse remodeling" is a time dependent phenomenon. It has been demonstrated that after the initial administration of metoprolol there is transient decrease LVEF within 24 hours followed by a progressive increase in LVEF over one to three months [12]. These changes were associated with a decrease in left ventricular mass and a transformation of the left ventricle to one that is more ellipsoidal, a ventricular shape that is more efficient. The precise time course of this improvement is not known, but there is evidence to suggest that it continues for at least six months. Comparison of the haemodynamic effects of metoprolol and carvedilol over a 13 to 15 month period reported similar clinical benefit [13]. There was evidence for a greater improvement in LVEF and in PCWP at both rest and exercise with carvedilol. In contrast metoprolol was associated with a greater increase in maximal exercise performance than carvedilol.

Although the effect of BB on LVEF is similar, their effect on cardiac beta-receptors sensitivity is not. Therapy with selective $beta_1$-receptor blockers like metoprolol and bisoprolol increase beta-receptor sensitivity whereas carvedilol a non-selective BB with alpha blocking properties does not effect $beta_1$-receptor sensitivity [9]. It is possible that this explains the differential effects of metoprolol and carvedilol on exercise performance that has been observed in some studies. Although not consistent, metoprolol has been observed in some studies to improve exercise performance [13], whereas carvedilol has consistently failed to show any exercise improvement [14]. More importantly this difference in $beta_1$-receptor sensitivity may become important in the setting of worsening heart failure that can occur in the setting of BB therapy. Dobutamine infusion in patients receiving long term therapy with metoprolol demonstrates an increase in cardiac function and LVEF [15]. This effect was related to the up-regulation of $beta_1$-receptor sensitivity associated with metoprolol therapy and which is not observed after chronic carvedilol.

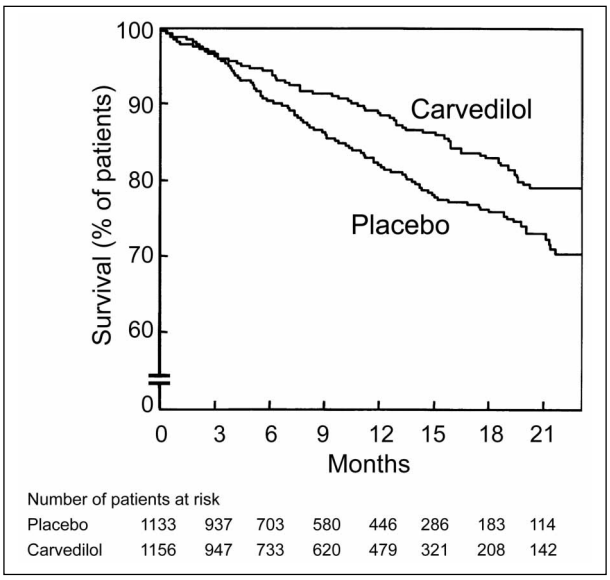

Figure 1. Kaplan-Meier analysis of time to death in the placebo group and the carvedilol group (all cause mortality; COPERNICUS). The 35 % lower risk in the carvedilol group was significant: p = 0.00013 (unadjusted) and p = 0.0014 (adjusted). From [4], Copyright © 2001 Massachusetts Medical Society. All rights reserved.

Randomized Clinical Trials in Severe Heart Failure

The initial US Carvedilol Program [14] was designed as group of four separate studies to examine the effect of carvedilol on exercise performance in a broad spectrum of patients with heart failure. That study failed to demonstrate any benefit of the drug on exercise performance but it did observe a composite decrease in mortality and hospitalization. The subsequent COPERNICUS trial [4] was designed specifically to examine the effect of carvedilol in patients with

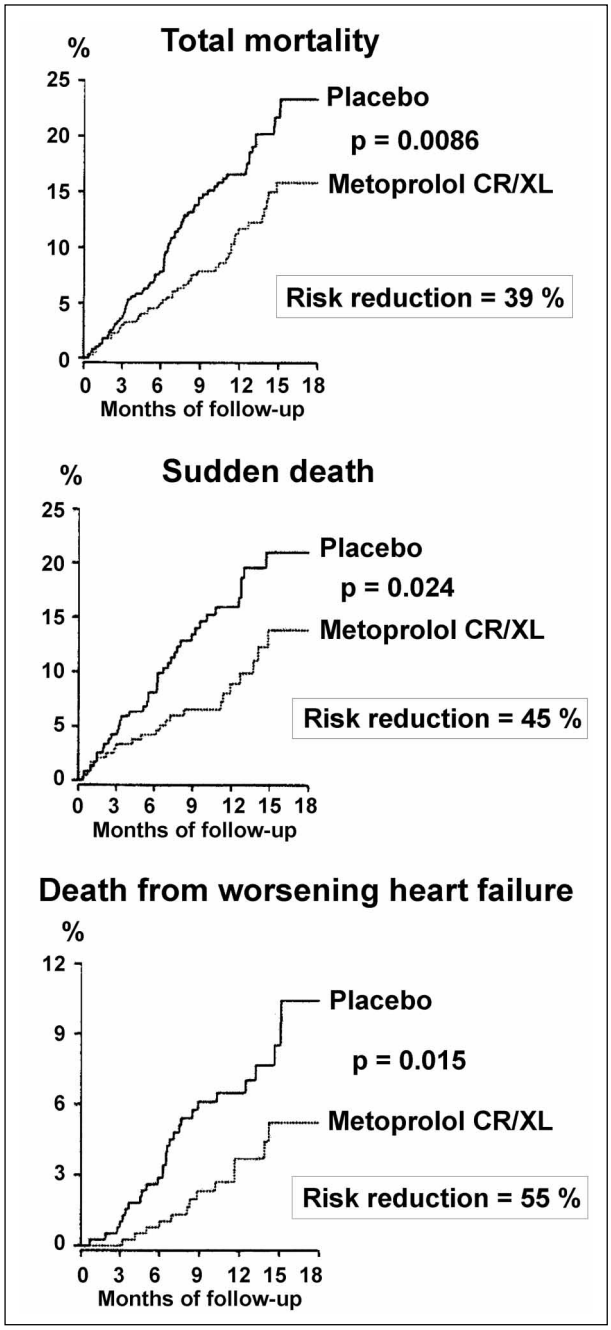

Figure 2. Kaplan-Meier curves of cumulative percentage of all-cause mortality (top), sudden deaths (middle) and deaths from worsening heart failure (bottom). CR/XL = controlled release/ extended release. Reprinted with permission from the American College of Cardiology Foundation from [16]

severe heart failure. It enrolled 2289 patients with severe heart failure characterized as having symptoms at rest or with minimal exertion with LVEF < 25 % (Fig. 1) and demonstrated a 35 % decrease in mortality (CI 19 to 48 %; p = 0.0014). The placebo population had an annual mortality of 19.7 % and a mean LVEF of 20 %. The results were consistent across all the pre-specified characteristics, and the drug was well tolerated.

Sub-group analysis of patients similar to COPERNICUS included in MERIT-HF [16] was carried out in order to confirm the findings of COPERNICUS. MERIT-HF [1] investigated Metoprolol CR/XL (controlled release/extended release) a long acting preparation of metoprolol succinate, a $beta_1$-receptor blocker in a broader spectrum of patients in NYHA Class II–IV with LVEF ≤ 40 %.

Sub-group analysis of NYHA III/IV of < 25 % in MERIT-HF observed a 39 % decrease in total mortality (Fig. 2) [16]. Comparison of the patients' characteristics and mortality benefit in the three trials investigating beta-blocker therapy in severe heart failure is shown in Figure 3.

In the MERIT-HF severe heart failure sub-group, not only did metoprolol CR/XL decrease total mortality by 39 %, it also decreased death due to worsening heart failure by 55 % and sudden death by 45 % (Fig. 2). In addition metoprolol CR/XL decreased the combined end-point of all cause mortality and all cause hospitalization by 29 %. The drug was well tolerated with 31 % fewer all cause withdrawals and 49 % fewer withdrawals due to worsening heart failure in the metoprolol CR/XL group compared to the placebo population (Fig. 4). Metoprolol CR/XL therapy also resulted in an improvement in NYHA functional class (p = 0.0031) compared to placebo.

In contrast, the Beta-blocker Evaluation Survival Trial (BEST) [17] which studied the effect of a non-selective beta-blocker bucindolol in a relatively high risk group of NYHA III and IV patients with LVEF ≤ 35 % failed to find a significant benefit although it trended positive. Bucindolol is the only beta-blocker that decreases plasma norepinephrine [18]. Since the patients enrolled in BEST had more advanced heart failure it is possible that some of the patients were dependent on chronic norepinephrine stimulation in order to maintain cardiac function.

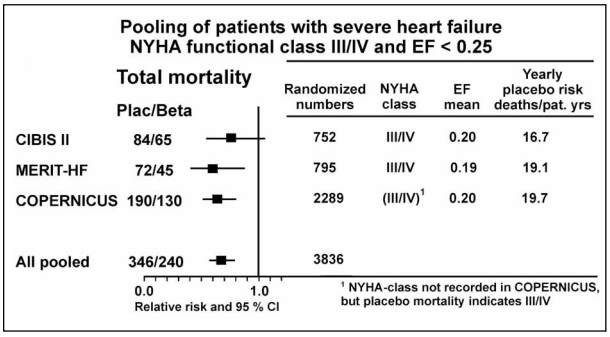

Figure 3. Point estimates for hazard ratios and 95 % confidence intervals for total mortality for subgroups of patients with severe heart failure (New York Heart Association [NYHA] functional class III/IV and ejection fraction [EF] < 0.25) in the CIBIS II study and the MERIT-HF study. Data for the COPERNICUS trial are also given together with pooled data. Number of deaths and number of patients in each randomization group, mean EF and yearly placebo (Plac) risk defined as deaths/patient years of follow-up are also given by study and for the pooled data. CI = confidence interval; n = 3,836. Reprinted with permission from the American College of Cardiology Foundation from [16]

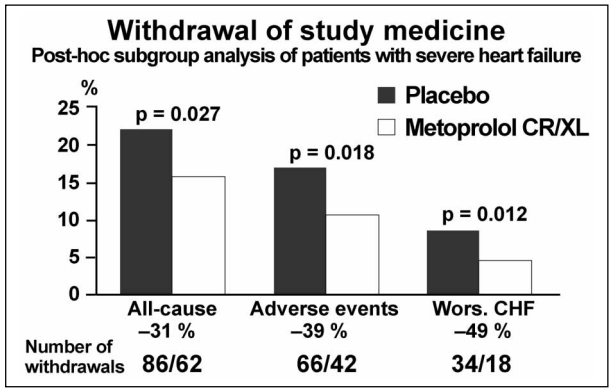

Figure 4. Total number of patients with permanent withdrawal of study drug due to any cause, due to any adverse event and due to worsening heart failure in the two randomization groups. Percentage figures are normalized for patient years of follow-up. CHF = chronic heart failure; CR/XL = controlled release/extended release. Reprinted with permission from the American College of Cardiology Foundation from [16]

Discussion

These studies indicate that BB are not only safe for the treatment of severe heart failure, but they are also extremely effective in decreasing mortality and the need for hospitalization. It is also clear that BB therapy provides an incremental benefit to standard ACEI therapy. It must be emphasized however that although the patients enrolled in these trials were classified as experiencing severe heart failure, they were for the most part stable on ACEI and without severe fluid overload. In addition most of the patients were ambulatory with stable blood pressure >100 mmHg. Whether or not BB therapy has a role in the more compromised heart failure patients with fluid overload and hypotension remains to be studied. At the present time a series of studies are underway to evaluate the role of temporary intravenous support with inotropic agents as a bridge to BB therapy in patients with more advanced heart failure who are haemodynamically unstable [19].

These studies are important in demonstrating the safety of BB in this defined population with severe heart failure. These observations should allay any concerns that physicians might have about the potential risk of BB in patients with heart failure. The demonstration that fewer adverse effects occurred in the BB treated patients than in the placebo group in these randomized controlled studies is important since, worsening heart failure events can occur at any time in the course of heart failure. Only in placebo controlled trials like these can the drug effects be differentiated from the naturally occurring events. The safety and benefit in these severe heart failure patients should encourage physicians to use them more widely in less severe patients with NYHA Class II and III. Although they have a lower mortality rate they represent the vast majority of patients in heart failure. The relative benefit of BB in NYHA Class II–III patients is similar to the higher risk group but the absolute benefit is much greater. These observations emphasize the major advance that has occurred in the last decade and particularly the incremental benefit of the addition of BB to therapy with ACEI.

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