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F. Waagstein

Update on Beta-Blockers in Congestive Heart Failure

Introduction

Beta-blockers which were earlier considered to be pure negative inotropic drugs have until recently been contraindicated for treatment of congestive heart failure. This has been the case despite the fact that the concept presented more than 25 years ago as an option for treatment in idiopathic dilated cardiomyopathy with tachycardia later followed by several small long-term studies confirming their ability to improve cardiac function and reduce symptoms. The original rationale for the concept was restoration of myocardial energy balance by reducing cardiac work, mainly by normalizing heart rate. This hypothesis has been confirmed later in clinical and experimental studies but several other mechanisms seem to play a role, such as interaction with other neurohormones, restoration of imbalance between vagal and sympathetic innervation of the heart, reduction of apoptosis and oxidative stress leading to slower disease progression and restoring electrical stability implying lower risk of sudden death.

Three large placebo-controlled randomised trials have now finally proven that three different beta-blockers, on top of ACE-inhibitors, reduce both cardiovascular morbidity and mortality in mild, moderate and severe heart failure.

Effect on cardiac function and exercise capacity

Numerous controlled studies have consistently shown improvement in ejection fraction, which exceeds the combined effects of digoxin and ACE-inhibitors. Diastolic function is improved similarly and preceeds improvement in systolic function. Reversed remodelling has been shown both with metoprolol and carvedilol occuring after 6 months of treatment and seems to be greater than with ACE-inhibitors alone. The effect on exercise capacity is less clear but there may be a somewhat better effect with the beta$_1$-selective blocker metoprolol compared to the non-selective beta-blockers carvedilol and bucindolol. This may be a consequence of less reduction of peak exercise heart rate with metoprolol possibly related to upregulation of beta-adrenergic receptors by metoprolol in contrast to absence of upregulation with carvedilol and bucindolol.

Effect on morbidity and mortality

Three large prospective randomised survival trials have now consistently shown a reduction in mortality by 34–35 % [1–3] (Figs. 1, 2, table 1). Two trials, CIBIS II and COPERNICUS, using bisoprolol and carvedilol included only more severely ill patients in NYHA class III–IV, whereas the MERIT-HF trial also included NYHA class II patients. All studies showed reduction of cardiovascular morbidity [1, 4] reflected as fewer re-admissions to hospital for cardiovascular reasons as well as fewer days in hospital. A retrospective analysis from the CIBIS II and the MERIT-HF trials using the same inclusion criteria as in the COPERNICUS trial, ejection fraction ≤ 0.25 and NYHA class III and IV showed similar average ejection fraction and placebo mortality indicating that these subsets of patients matched well the patients included in the COPERNICUS trial. Moreover, reduction in mortality in the MERIT-HF subset of patients were of the same order as in the COPERNICUS trial, 39 % vs 35 %, and for morbidity all cause 25 % vs 20 %, for cardiovascular cause 32 % vs 28 % and for heart failure cause 44 % vs 33 % indicating a strong benefit of metoprolol also in more severe heart failure patients. A fourth trial [5] in patients with severe heart failure (BEST), did not show a significant reduction in all-cause mortality, although a significant reduction in cardiovascular death and heart transplantation or death was observed. The reason for discrepancy between this trial and the other three trials remains obscure, but too strong beta$_2$-blocking effect reducing norepinephrine release too markedly in the more severe heart failure patients has been a proposed explanation [5].

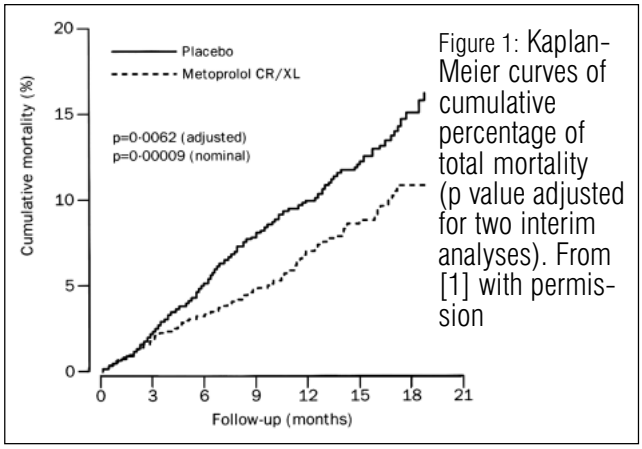

Figure 1: Kaplan-Meier curves of cumulative percentage of total mortality (p value adjusted for two interim analyses). From [1] with permission

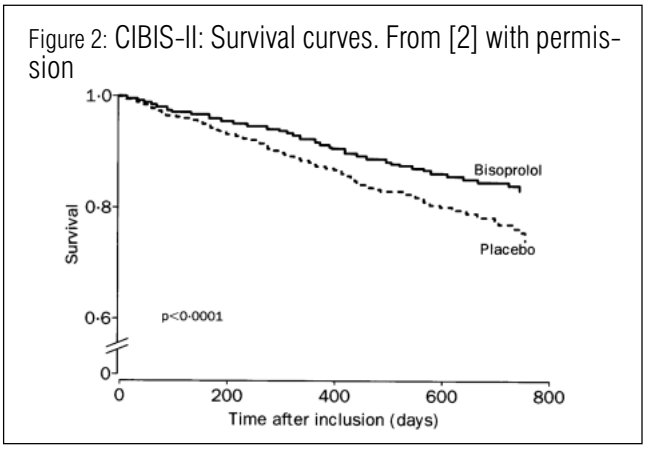

Figure 2: CIBIS-II: Survival curves. From [2] with permission

How to use beta-blockers in CHF

When initiating beta-blockade in congestive heart failure it is important to start with a low dose and increase the dose slowly over 6–8 weeks in order to allow the circulation to adapt to reduction of cardiac sympathetic drive caused by blockade of myocardial beta-adrenergic receptors. The starting dose ranges from 1/8 to 1/16 of the target dose depending on the severity of heart failure. Initial systolic blood pressure should be ≥ 100 mmHg. In case it is not, one should consider lowering the ACE-inhibitor dose in order to obtain an appropriate blood pressure allowing initiation of the beta-blocker. A reduction in the ACE-inhibitor dose from target dose does not seem to reduce the effect on mortality significantly according to the ATLAS study [6], whereas the strong beneficial effect on mortality from beta-blockade would be missed if the patient does not receive a beta-blocker. The data base from all three beta-blocker mega trials show clearly that withdrawal of beta-blockade for cardiovascular reasons like bradycardia, hypotension or increase in congestive heart failure is rare since it occurs as often or more frequently in the placebo treated patients. This indicates a high degree of safety with these drugs. Also for adverse events related to respiratory disease, psychiatric disorders or diabetes no increase was seen with metoprolol. As a rule, the final dose of beta-blockers should be the target dose for these trials. If, however, the final dose is lower than the target dose for reasons like hypotension, bradycardia or marked fatigue, the lower dose would also significantly reduce morbidity and mortality according to retrospective analysis of MERIT-HF [7]. The subset of patients not tolerating a target dose of metoprolol in that study were sicker than those tolerating the target dose, as reflected by a higher placebo mortality. Despite this the withdrawal rate for cardiovascular reasons, was even more markedly reduced by metoprolol compared to patients receiving the target dose. This indicates the importance of trying to treat also these patients since the high mortality rate in this patient group implies that more lifes could be saved per treated patient years than in patients with lower risk.

Table 1: Overview: Effects of Metoprolol CR/XL on endpoints (MERIT-HF trial)

Primary endpoints		
• Total mortality	**–34 %**	p = 0.0062
• Total mortality or all cause hospitalization	**–19 %**	p = 0.0001
Secondary endpoints		
• Total mortality or hospitalization due to worsening CHF	**–31 %**	p < 0.0001
• Death or heart transplantation	**–32 %**	p = 0.0002
• Cardiovascular mortality	**–38 %**	p < 0.0001
• Sudden death	**–41 %**	p = 0.0002
• Death from worsening CHF	**–49 %**	p = 0.0023
Tertiary endpoints		
• Total mortality or hospitalization or emergency department visit due to worsening CHF	**–32 %**	p < 0.0001

Conclusion

It can now be finally stated that beta-blockers should be given in addition to ACE-inhibitors to all haemodynamically stable patients with congestive heart failure due to primarily systolic dysfunction regardless of severity of disease. Due to their effectiveness in NYHA class II as demonstrated with metoprolol in the MERIT-HF trial it is important to start treatment as early as possible after diagnosis to prevent sudden death, which is the predominant cause of death in NYHA class II and III patients, as well as preventing progression of disease into more severe heart failure. The common denominator for the beta-blockers used in the three survival trials showing almost identical effects on mortality and morbidity, is $beta_1$-adrenergic receptor blockade, which raises the question whether $beta_2$- and $alpha_1$-blockade give additional benefit. The experience from the BEST trial with bucindolol emphazises that only beta-blockers proven to be beneficial in controlled trials should be used for treatment in heart failure.

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