

The Role of Beta Blockade in Heart Failure

a report by

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Beta-blocker therapy remains one of the most fascinating issues in heart failure (HF) clinical practice. These agents, once absolutely contraindicated in patients with HF, have been shown to have the greatest beneficial effects on the patients' prognosis. They have radically changed the clinical course of HF, more than any other agent previously introduced, and are now the cornerstone of current HF treatment.¹⁻³ Beta-blocker therapy contradicted most of the hypotheses on which the treatment of HF was based. The long-term improvement in left ventricular (LV) function and prognosis after beta-blocker treatment definitively showed that:

- HF is a progressive disease whose long-term clinical course may be changed; and
- the excessive cardiac sympathetic drive, rather than abnormal haemodynamics, was the main determinant of the clinical course.⁴⁻⁶

Clinical Effects

Swedish authors were the first to show, in 1975, the beneficial effects of beta-blockade in HF patients.⁷ Further studies from the same group showed that long-term beta-blocker therapy may improve LV systolic and diastolic function and, even more importantly, may improve survival.^{8,9} It is impressive how this last study, including only 36 patients, could show such an effect and predict the results of trials concluded almost 20 years later (see *Figure 1*). Concomitant analyses of the major post-infarction trials showed that beta-blockade had its greatest effects among the patients with signs of HF or of LV dysfunction.^{10,11}

In the following years, controlled trials showed the beneficial effects of beta-blockers on LV function and the clinical course of patients with chronic HF.¹²⁻¹⁶ Beta-blockers were more effective than angiotensin-converting enzyme (ACE) inhibitors at reversing LV remodelling, with an improvement in LV ejection fraction (EF), a decline in LV volumes, reduced severity of mitral regurgitation and a less spherical LV shape.¹³⁻¹⁸ These changes are secondary

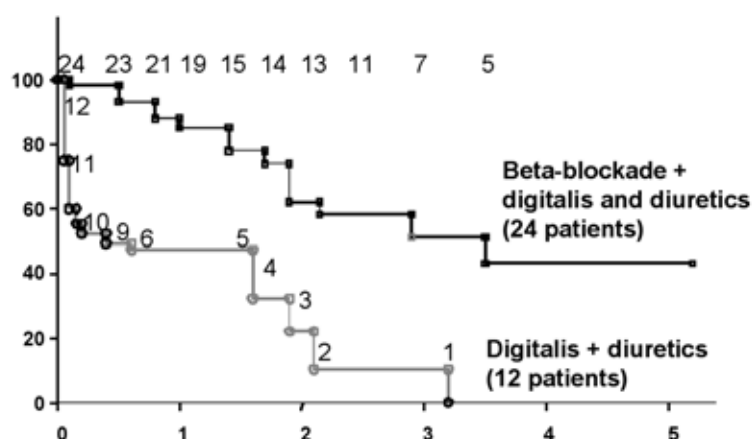
to the beneficial effects of beta-blockade on the intrinsic mechanisms leading to progressive myocardial degeneration.^{5,15} They include changes in myocardial metabolism,^{14,15,18} myocardial contractile protein isoforms, sarcoplasmic reticulum calcium-dependent ATPase (SERCA) activity and gene expression,¹⁹ and ryanodine receptor phosphorylation.²⁰ In turn, LV inverse remodelling by beta-blocker therapy may further contribute to the overall improvement in LV function.⁴

Large multicentre controlled clinical trials showed the beneficial effects of beta-blocker treatment on prognosis. All-cause and cardiovascular (CV) mortality, as well as all-cause, CV and worsening HF hospitalisations, were reduced by beta-blocker treatment, compared with placebo, in landmark trials (see *Table 1*).²¹⁻²⁴ The effects on survival were additive to that of ACE inhibitors and were of greater magnitude compared with those previously found with them.⁵

The first mortality trials included patients with LV systolic dysfunction, shown by a low EF and mild to moderate HF. This was shown by the relatively low annual mortality of the placebo-treated patients (13.2% in the Cardiac Insufficiency Bisoprolol Study II (CIBIS-II) and 11% in Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF)).^{22,23} The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) broadened the indications to beta-blocker therapy. It included patients with symptoms at rest or minimal exertion and severe LV dysfunction (EF of less than 25%). Accordingly, the mortality of the placebo treated patients was higher (18.5%). Carvedilol was associated with a significant 35% reduction in all-cause mortality (relative risk (RR), 0.65; 95% confidence interval (CI), 0.81-0.52; $p=0.0014$) and with a 24% reduction in the combined end-point of death and hospitalisations (RR, 0.76; 95% CI, 0.67-0.87).²⁴ Carvedilol was associated with an excellent tolerability with a similar incidence of side effects and early (two weeks after study initiation) beneficial effects on prognosis, compared with placebo.²⁵ Carvedilol was also associated with a reduction in mortality, compared



Figure 1: Prolongation of Survival in Dilated Cardiomyopathy by Beta-receptor Blockade



Redrawn with permission from reference 9.

Table 1: Per Cent Reduction in Major Events in Randomised Controlled Beta-blocker Heart Failure Mortality Trials Showing Beneficial Effects of the Active Agents²¹⁻²³

Trial (year)	CIBIS-II (1999)	MERIT-HF (1999)	COPERNICUS (2001)
Active agent	bisoprolol	metoprolol succinate	carvedilol
All-cause mortality	-34%	-34%	-35%
Sudden death	-44%	-41%	-44%
All hospitalisations	-20%	-18%	-20%
HF hospitalisations	-32%	-35%	-33%

CIBIS-II = the Cardiac Insufficiency Bisoprolol Study II; MERIT-HF = Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure; COPERNICUS = The Carvedilol Prospective Randomized Cumulative Survival; HF = heart failure.

with placebo, in patients with early post-infarction LV dysfunction, with or without symptoms, in the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial.²⁶

The Benefits of Anti-adrenergic Therapy

The effects of increased sympathetic drive in the failing heart are complex. Beta-adrenergic stimulation causes major changes both in the characteristics of the myocytes (foetal gene expression, abnormal calcium handling, abnormal metabolism) and in their number, with an acceleration of cell death through the mechanisms of ischaemic necrosis and apoptosis.^{5,18} In the short term, it also increases myocardial contractility so that in advanced HF, the heart may be critically dependent on adrenergic drive. Not all the beta-adrenergic-mediated mechanisms are deleterious. For instance, phospholamban inhibition with a secondary increase in SERCA activity may increase myocardial contractility.²⁷

On the other hand, the pharmacological characteristics of anti-adrenergic agents may also differ. Beta-blocking agents with intrinsic sympathomimetic activity, such as xamoterol, have

increased, rather than reduced, mortality in patients with HF,²⁸ an effect related to increased sympathetic drive, mainly at night time.

Bucindolol, a non-selective beta1- and beta2-receptor blocker, has had a neutral effect on mortality in a large multicentre trial (RR, 0.90; 95% CI, 0.78–1.02; p=0.13).²⁹ This result may be explained by the characteristics both of the patients studied (high prevalence of black patients and of patients with advanced HF) and of bucindolol itself. Bucindolol inhibition of norepinephrine release from pre-synaptic nerve endings, an effect mediated by pre-synaptic beta-2 receptor blockade, may be deleterious in patients with advanced HF and/or with other characteristics.³⁰

Similarly, unfavourable results have been obtained with agents that inhibit pre-synaptic norepinephrine release, acting as agonists of the imidazoline receptors. Moxonidine administration to patients with HF has been associated with a dose-related increase in the mortality and hospitalisation rate.³¹ The Moxonidine Congestive Heart Failure (MOXCON) trial was prematurely stopped after the inclusion of 1,934 patients for an early increase in mortality and adverse events in the moxonidine SR group. The mortality rate was 5.5% in the moxonidine SR group and 3.4% in the placebo group (p=0.012). Hospitalisation for HF, acute myocardial infarction (MI) and adverse events was also more frequent in the moxonidine SR group. Plasma norepinephrine was significantly decreased by moxonidine SR (-18.8% from baseline) compared with placebo (+6.9%).³²

The Clinical Importance of the Differences Between Beta-blockers

Previous studies have already showed that the pharmacological characteristics of antiadrenergic agents may influence their effects on survival. Both agents with intrinsic sympathomimetic activity and agents decreasing norepinephrine release are associated with untoward effects on survival – the first because of excessive sympathetic stimulation, the others, likely, because they blunt sympathetic response when an increase in myocardial contractility and blood pressure would be necessary, such as during exercise, stress or arrhythmias.

It remained uncertain whether there could be differences in the magnitude of the effects on mortality between beta-blockers that are both associated with favourable effects on outcome. This hypothesis was tested in the Carvedilol or Metoprolol European trial (COMET). Three thousand and twenty-nine patients with II–IV New York Heart Association (NYHA) class HF, an LV EF less than 35%, a CV hospitalisation in the previous

two years and on standard treatment with diuretics and ACE inhibitors, were randomised to either carvedilol, titrated up to 25mg bid, or metoprolol tartrate, titrated to up to 50mg bid. COMET was an event-driven trial designed to end when 1,020 deaths had occurred. The average follow-up was long (57.9 months) making it one of the largest and longest trials of CHF patients.³³

In COMET, carvedilol treatment was associated with a significant 17% reduction in all-cause mortality (RR, 0.83; 95% CI 0.74–0.93; $p=0.0017$), compared with metoprolol tartrate. The annual mortality rate was reduced from 10% to 8.3% and calculated median survival was prolonged by 1.4 years with carvedilol. The distribution of the mode of death was similar with both treatments. The reduction of sudden death rate was significant with carvedilol compared with metoprolol (RR, 0.81; 95% CI, 0.68–0.97; $p=0.022$). The reduction of circulatory failure death was of similar magnitude although it did not reach statistical significance because of the lower number of events (RR, 0.83; 95% CI, 0.67–1.02; $p=0.07$).³³ Significant differences were found in other end points including those related to vascular events such as MI and stroke (see Figure 2). The other co-primary end-point of all-cause mortality and all-cause-hospitalisation was reached by 73.9% of patients on carvedilol and 76.4% on metoprolol with no difference between the two groups (HR, 0.937; 95% CI, 0.863–1.017; $p=0.1219$). The incidence of hospitalisations was, in fact, similar between the patients on carvedilol and those on metoprolol tartrate.³³ (The explanation of this finding is that the lower mortality of the patients on carvedilol exposed them to an increased risk of hospitalisations.)

COMET supports the hypothesis that meaningful differences exist in the clinical effects of different beta-blockers in CHF. The superiority of carvedilol, compared with metoprolol tartrate, at the doses and modes of administration used in this trial, was clearly shown. Only the beta-blockers associated with favourable effects on mortality, carvedilol, bisoprolol and metoprolol succinate, and not metoprolol tartrate, should be used in the patients with HF.³ According to some authors, the results of COMET should be ascribed to methodological issues and, namely, to the administration of relatively low doses of metoprolol tartrate with less beta-1 receptor blockade. Post-hoc analyses have shown that the differences in outcome between carvedilol and metoprolol tartrate were independent of beta-blocker doses, heart rate and blood pressure changes.³⁴ Moreover, single centre comparison trials have shown a greater improvement from baseline in LV function with carvedilol, compared with metoprolol tartrate, even when the latter had been administered at higher doses than in COMET.³⁵ A final answer to this issue is not possible based on the

Figure 2: Relative Risk of Primary End-points, Causes of Deaths and Cardiovascular End-points with Carvedilol Versus Metoprolol Tartrate in the COMET Trial

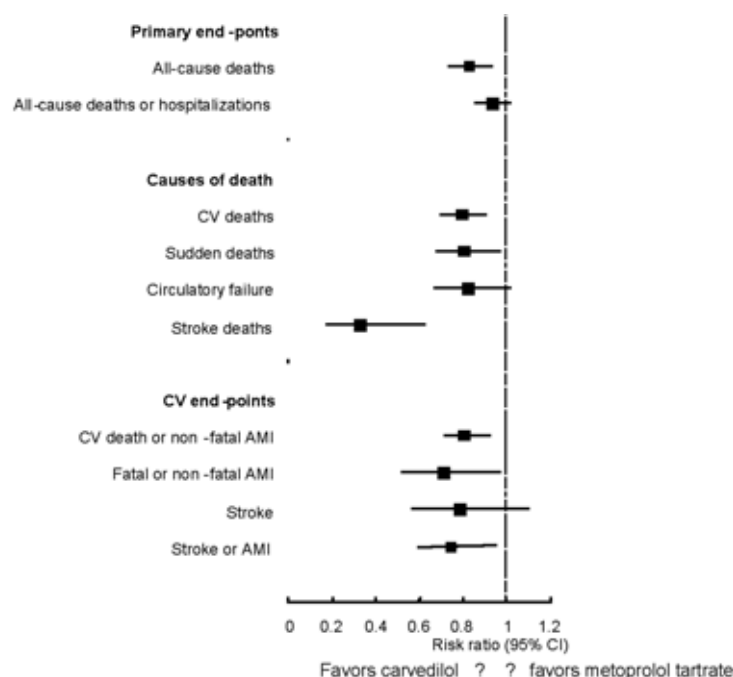


Table 2: Specific Pharmacological Characteristics of Carvedilol

- Beta2-adrenergic receptors blockade (5,18,35,37)
- Alpha-1 adrenergic receptor blockade (5,18,35,37)
- Anti-endothelin effects (38)
- Anti-oxidant activity (18,35)
- Longer and tighter binding to beta-1 adrenergic receptors (39)
- Beta-2 adrenergic receptors inverse agonistic activity (40)

data from COMET; however, it should be noted that its results are also consistent with many specific pharmacological characteristics of carvedilol, which may be useful for the treatment of HF.^{5,18,36–40} These characteristics are summarised in Table 2.

Implementing Beta-blocker Treatment – Treating Co-morbidities and Disease Management Programmes

Beta-blockers now have a pivotal role in the treatment of chronic HF;^{1–3,5,41} however, they are still significantly underused. Recent international surveys show that these drugs are administered to only a minority of the HF patients, with percentages of 34% and of 36.9% in the IMPROVEMENT and EuroHeart surveys, respectively.^{42,43} The doses of the beta-blockers are also significantly lower than those used in controlled clinical trials: metoprolol, 74.9±43.3mg, daily; carvedilol, 17.6±16.6mg, daily; bisoprolol 4.7±2.6mg, daily.⁴³

Factors associated with impaired tolerance to beta-blocker therapy are increased age, renal insufficiency, hypotension and more severe HF.⁴⁴ The percentages

of patients with traditional contraindications who do not tolerate beta-blockers is generally low.⁴⁴ Retrospective analyses of randomised trials have shown that the efficacy and tolerability of beta-blocker therapy are independent of factors like sex⁴⁵ and diabetes.⁴⁶ Elderly patients and patients with advanced HF have a lower tolerability but may benefit from beta-blocker therapy to a similar extent as younger patients.^{47–49} In the recent Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with heart failure (SENIORS) trial the administration of the beta-blocker nebivolol to elderly patients (more than 70 years) with chronic HF was associated with a 14% reduction in all-cause mortality or CV hospitalisations (RR, 0.86, 95% CI 0.74–0.99; $P = 0.039$) with a non-significant trend to reduced mortality (HR 0.88, 95% CI 0.71–1.08; $P = 0.21$).⁴⁸ The limitation of chronic obstructive pulmonary disease with asthma may be partially overcome by the use of beta-1 selective agents or by agents with concomitant alpha-blocking (and thus bronchodilating) activity;⁵¹ however, bradycardia and asthma remain the most important contraindications to beta-blockade.^{43,44,52}

Recent studies have shown the importance of patients' follow-up in specialised centres. The Bring-up study was an Italian programme finalised at the implementation of beta-blocker therapy. The percentage of patients on beta-blockade increased from 24.9% to 57.6% at the end of the first year of study with 70% of the patients reaching target beta-blockers doses.⁵² Other modalities of implementation of beta-blocker therapy have been recently proposed.

These include its early initiation during a hospitalisation for HF. A strategy of pre-discharge initiation of beta-blocker therapy was associated with a higher percentage of patients on beta-blockers (91.2% compared with 74.1%) with higher maintenance doses and without any difference in the incidence of side effects.^{53,54}

It is now essential to extend beta-blocker therapy to the largest number of patients with HF, including the elderly and the patients with comorbidities. To achieve this, it is important that disease management systems which could allow the initiation and uptitration of treatment be established.

Conclusions

To date, beta-blockers are the most effective agents to improve LV function and prognosis of the patients with chronic HF. These drugs act on the intrinsic mechanisms causing LV dysfunction – thus their effects emerge slowly though they are then maintained, and even enhanced, in the long-term. Bisoprolol, carvedilol and metoprolol succinate have all been associated with a reduction in mortality and hospitalisations, compared with placebo. Nebivolol has also improved the outcome in elderly patients with chronic HF. As important differences exist between different beta-blockers, only the agents shown to be effective in randomised trials should be administered. The administration of beta-blocker therapy to the largest number of patients and their titration up to the target doses shown to be effective should be primary aims in the treatment of patients with HF. ■

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