Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Trial
Carvedilol as the Sun and Center of the β-Blocker World?
Kai C. Wollert, MD; Helmut Drexler, MD

Heart failure is a deadly disease that has reached epidemic proportions in industrialized countries. Patients living with heart failure carry a heavy burden in terms of morbidity. Many patients require repeated hospitalizations for cardiovascular problems, especially for episodes of worsening heart failure. In fact, heart failure is one of the most important causes of hospital admissions in the United States, accounting for over 2.5 million admissions per year. Once hospitalized, patients with heart failure have an increased risk of recurrent hospitalizations and death. Approximately 30% to 40% of patients are readmitted within 6 months of an index hospitalization. Angiotensin-converting enzyme (ACE) inhibitors, digitalis, and spironolactone decrease the risk of hospitalization in heart failure patients; however, the annual rate of hospital admission for worsening heart failure has remained high.1–3 Given these challenges, clinical trials conducted in the mid 1990s that demonstrated that β-blocker therapy in addition to ACE inhibitors and digitalis reduces the risk of hospitalization in heart failure patients by about 20% to 30% represented remarkable progress. These beneficial effects of β-blocking agents on morbidity were recognized well before favorable effects on survival were unequivocally established (Table). In some, but not all, trials, the clinical benefits of β-blocker treatment included improved heart failure symptoms as assessed by physicians and patients.

Previous trials addressing the effects of β-blockers on morbidity have been conducted in patients with mostly mild to moderate heart failure (Table). In the early stages of heart failure, slowing disease progression and increasing long-term survival are the primary objectives of any form of therapy. In severe heart failure with recurrent hospitalizations, keeping patients out of the hospital is an equally important treatment goal. However, the effects of β-blocking agents on morbidity in patients with severe heart failure have been less well established.

In this issue of Circulation, Milton Packer and colleagues present a comprehensive analysis of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial database, looking at the effects of the β-blocker carvedilol on morbidity (as defined by the need for hospital admission) in patients with severe heart failure. The COPERNICUS trial was a prospective, double-blind, placebo-controlled trial designed to evaluate the effects of carvedilol on mortality (the primary endpoint) and morbidity in patients with severe heart failure, as defined by dyspnea or fatigue at rest or on minimal exertion, and a left ventricular ejection fraction of less than 25% despite conventional therapy with diuretics and an ACE inhibitor or angiotensin II antagonist. Patients requiring intensive care, intravenous inotropic agents, or vasodilators and patients with marked fluid retention were not included in the trial. As previously reported, the trial was stopped early after a mean duration of follow-up of 10.4 months because of a highly significant beneficial effect of carvedilol on survival. The effects of carvedilol on morbidity endpoints in patients with severe heart failure may be summarized as follows. In the placebo group, 38.1% of patients required hospitalization for any reason, and 23.7% of the total placebo group were hospitalized for worsening heart failure. Considering the short duration of follow-up, these numbers are striking and illustrate the facts that patients in the COPERNICUS trial truly had severe heart failure and many patients had significant co-morbidities. In the carvedilol group, 32.2% of patients required hospitalization for any reason, and only 17.1% were hospitalized for worsening heart failure, reflecting a highly significant beneficial effect of carvedilol on the risk of hospitalization. Overall, patients in the carvedilol arm of the COPERNICUS trial spent 27% fewer days in the hospital for any reason and 40% fewer days in the hospital for heart failure. These differences were due both to a decrease in the number of hospitalizations and to a shorter duration of each admission. Importantly, there appeared to be no early increase in the risk of hospitalization for heart failure or other serious cardiovascular events after initiation of carvedilol, even though patients had advanced disease. These data are impressive and indicate that, similar to patients in the earlier stages of the disease, patients with severe heart failure derive substantial benefit from anti-adrenergic therapy not only in terms of reduced mortality but also reduced morbidity.

Not all β-blockers are created equal. Most notably, distinct β-blocking agents differ in their specific adrenergic receptor blocking profiles and the presence or absence of ancillary properties. Because chronic β1-adrenergic receptor signaling is the dominant cardiotoxic pathway in the failing heart,
effective β₁-adrenergic receptor blockade is thought to be especially important. The increased mortality with xamoterol and the recent disappointing results with bucindolol remind us that clinical outcomes may be poor with certain β-blockers. Although not discussed by Packer et al., both “second-generation” β₁-selective compounds (bisoprolol and metoprolol) and the “third-generation” non-selective β₁/β₂/β₃-blocker carvedilol have been shown to reduce all-cause mortality and the risk of hospitalization in heart failure patients. In addition to their established antiarrhythmic and anti-ischemic properties, general mechanisms through which these β-blocking agents reduce heart failure mortality and morbidity likely involve their salutary effects on progressive left ventricular remodeling and functional deterioration. As outlined in the Table, the impact of bisoprolol and metoprolol on mortality and morbidity in patients with moderate heart failure was approximately in the same range as observed for carvedilol in patients with moderate and severe heart failure. A recent post hoc analysis of the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) indicates that metoprolol exerts favorable mortality and morbidity effects in severe heart failure as well. From a clinical standpoint, only direct head-to-head comparisons will answer the question of whether any particular β-blocker offers advantages over others. In the ongoing Carvedilol or Metoprolol European Trial (COMET), 3029 patients with moderate or severe heart failure have been randomized to metoprolol tartrate (target dose 50 mg BID) or to carvedilol (target dose 25 mg BID). This trial was designed to answer the question of whether β-blocking agents with differing pharmacological profiles exert different effects on heart failure mortality and morbidity. The end of this trial is anticipated to be in November 2002, and the results are eagerly awaited. This trial, however, does not address the possibility that the controlled release/extended release formulation of metoprolol, which was used in MERIT-HF, may be superior to the immediate release metoprolol tartrate formulation.

In the future, our most important goal may be to bridge the gap between the wealth of knowledge that has been derived from clinical heart failure trials and the less-than-perfect way many heart failure patients are still being treated in the community. The implementation of treatment strategies with proven efficacy in the medical community requires education of both healthcare providers and patients. In addition, multidisciplinary disease management programs have the potential to augment the effectiveness of pharmacological therapy and to help heart failure patients stay out of the hospital.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Agent</th>
<th>n</th>
<th>Primary Endpoints</th>
<th>Population</th>
<th>Morbidity Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDC</td>
<td>Metoprolol</td>
<td>383</td>
<td>Mortality/need for Tx (−34%, P=0.056)</td>
<td>DCM</td>
<td>−33% HA, HF/arrhythmias NYHA ↓, QOL ↑</td>
</tr>
<tr>
<td>CIBIS</td>
<td>Bisoprolol</td>
<td>641</td>
<td>Mortality (−20%, P=0.22)</td>
<td>mean EF 25%</td>
<td>−32% HA for HF NYHA ↓</td>
</tr>
<tr>
<td>US HF study group</td>
<td>Carvedilol</td>
<td>1094</td>
<td>Submax exercise ↔</td>
<td>mean EF 23%</td>
<td>−29% HA, any NYHA ↓</td>
</tr>
<tr>
<td>ANZ HF I/II</td>
<td>Carvedilol</td>
<td>415</td>
<td>EF +5.3% Max exercise ↔</td>
<td>mean EF 29%</td>
<td>−23% HA, any NYHA ↑/↓ patients felt unchanged</td>
</tr>
<tr>
<td>BEST</td>
<td>Bisoprolol</td>
<td>2647</td>
<td>Mortality (−32%, P&lt;0.0001)</td>
<td>mean EF 28%</td>
<td>−20% HA, any NYHA ↓</td>
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<tr>
<td>MERIT-HF</td>
<td>Metoprolol†</td>
<td>3991</td>
<td>Mortality (−34%, P&lt;0.0001)</td>
<td>mean EF 28%</td>
<td>−13% HA, any NYHA ↓</td>
</tr>
<tr>
<td>BEST</td>
<td>Bucindolol</td>
<td>2708</td>
<td>Mortality (−10%, P=0.13)</td>
<td>mean EF 23%</td>
<td>−6% HA, any NYHA ↓</td>
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<tr>
<td>COPERNICUS</td>
<td>Carvedilol</td>
<td>2289</td>
<td>Mortality (−35%, P=0.00013)</td>
<td>mean EF 20%</td>
<td>−20% HA, any NYHA ↓</td>
</tr>
<tr>
<td>COMET</td>
<td>Metoprolol* vs</td>
<td>3029</td>
<td>Mortality and morbidity EF&lt;35%</td>
<td>EF&lt;35% HA</td>
<td>ongoing trial</td>
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<tr>
<td></td>
<td>carvedilol</td>
<td></td>
<td></td>
<td>NYHA II–IV</td>
<td></td>
</tr>
</tbody>
</table>

HA indicates hospital admission; QOL, quality of life; Tx, cardiac transplantation; DCM, dilated cardiomyopathy; ICM, ischemic cardiomyopathy; EF, left ventricular ejection fraction; †, mortality; ↑, increased; ↓, decreased; ↔, no change; NYHA, New York Heart Association; MDC, Metoprolol in Dilated Cardiomyopathy; CIBIS, Cardiac Insufficiency Bisoprolol Study; HF, heart failure; ANZ HF, Australia-New Zealand Heart Failure research collaborative group; and BEST, Beta-blocker Evaluation of Survival Trial.

*Metoprolol tartrate; †Metoprolol CR/XL (controlled release/extended release).
References


Key Words: Editorials ▪ heart failure ▪ morbidity ▪ receptors, adrenergic, beta
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