Carvedilol reduced death and hospitalization in congestive heart failure

Objective
To determine the effectiveness of carvedilol on left ventricular ejection fraction (LVEF), symptoms, and mortality in patients with ischemia-related congestive heart failure (CHF).

Design
Randomized, double-blind, placebo-controlled trial.

Setting
20 hospitals in Australia and New Zealand.

Patients
415 patients (mean age 67 y, 80% men) with chronic stable CHF, with LVEF < 45%, and who were currently in New York Heart Association (NYHA) functional class II or III or previously in class II to IV. Exclusion criteria were current NYHA class IV CHF, heart rate < 50 beats/min, second- or third-degree heart block, blood pressure < 90 mm Hg systolic or > 160/100 mm Hg, treadmill exercise duration of < 2 or > 18 minutes, recent coronary event or procedure, primary myocardial infarction or valvular disease, diabetes, use of β-blockers or β-agonists, or other serious disease.

Intervention
Patients were assigned to carvedilol (n = 207) or placebo (n = 208) titrated from 3.125 mg to a maximum of 25 mg twice daily.

Main outcome measures
Primary outcomes were changes in LVEF and exercise treadmill duration. Secondary outcomes were changes in left ventricular size, 6-minute walking distance, symptoms of CHF, death, hospitalization, and worsening CHF.

Main results
At 12 months, LVEF in the carvedilol group improved to 5.3% more than that of the placebo group (P < 0.001). After a mean 19-month follow-up, fewer patients in the carvedilol group had the combined event of death or hospitalization (P = 0.02) or hospitalization alone (P = 0.05) (Table). The groups did not differ for mortality alone, individual causes of hospitalization, treadmill exercise duration or 6-minute walking distance, NYHA levels, symptoms of CHF, or worsening CHF.

Conclusion
In patients with ischemia-related CHF, carvedilol improved LVEF, left ventricular size, and combined mortality and hospitalizations but did not improve symptoms or exercise performance.

Abstract and Commentary also published in ACC Journal Club. 1997;127:3.

Carvedilol vs placebo*

<table>
<thead>
<tr>
<th>Outcome at 19 mo</th>
<th>Carvedilol EER</th>
<th>Placebo CER</th>
<th>RRR (95% CI)</th>
<th>ARR (EER – CER)</th>
<th>NNT (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or hospitalization</td>
<td>50%</td>
<td>63%</td>
<td>21% (6 to 34)</td>
<td>14%</td>
<td>8</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>48%</td>
<td>58%</td>
<td>18% (1 to 32)</td>
<td>10%</td>
<td>10</td>
</tr>
</tbody>
</table>

*Abbreviations defined in Glossary; RRR, ARR, NNT, and CI calculated from data in article.

Commentary
The use of β-blockers in CHF is expanding. We formerly believed them to be contraindicated, but these agents produce substantial benefit in carefully selected and monitored patients. Although other β-blockers, such as metoprolol, improve symptoms, exercise capacity, and left ventricular function, their effect on mortality remains unclear. Carvedilol has 2 distinctive ancillary properties of potential therapeutic importance: α-adrenergic blockade and antioxidant effects. This modest-sized study plus another report that was not designed to address mortality (1) indicate promise for carvedilol in CHF, including improvement of the composite event of death or hospitalization. However, the careful selection criteria and monitoring, along with early experience of worsening CHF in one third of the patients treated, raise important concerns regarding the general use of carvedilol (2). Moreover, the trend toward worsening symptoms within the first 6 months and the interesting dissociation between lack of functional improvement compared with a benefit in mortality and hospitalization remind us of the delicate balance between quality and quantity of life. In context, the trials of angiotensin-converting enzyme (ACE) inhibitors that showed unequivocal reduction in mortality in CHF were derived from experience in > 1300 deaths compared with approximately 100 deaths with carvedilol. Hence, quantitative estimates of mortality reduction based on current data for carvedilol are imprecise. These studies underscore enthusiasm for larger studies of carvedilol and other β-blockers that are primarily designed to address mortality.

For now, ACE inhibitors remain the therapy of choice for CHF; digitalis is reaffirmed as a safe therapy for symptom amelioration and reduced hospitalization rates, and diuretics are effective for circulatory congestion (3).