Heart failure has become one of the main causes of hospitalization for elderly patients, and carries a higher risk of mortality than many cancers. The total five-year mortality rate is nearly 50%. For functional class II or III patients, the annual mortality rate is nearly 15%.¹ In the past few years, randomized studies have clarified the place of various individual therapeutic approaches. For instance, studies

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**Breaking Down Beta-Blockers and Heart Failure**

Beta-blockers, which used to be contraindicated in heart failure, now form part of the standard therapeutic armamentarium and even represent the best approach in terms of absolute value.

By Michel Samson, MD

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have shown the following: improved survival with angiotensin-converting enzyme (ACE) inhibitors and aldactone; digitalis had little effect either way; and mortality increased with positively inotropic agents.

Although the negative inotropic effect of beta-blockers resulted in their contraindication in left ventricular dysfunction until very recently, there is now evidence that, not only are they tolerated, but they greatly improve prognosis. This article, therefore, deals with the pathophysiologic basis for their use. Details of relevant randomized studies during which beta-blockers have been administered will follow, together with differences between the beta-blockers studied. Lastly, their use will be discussed.

**Pathophysiology**

Left ventricular dysfunction results in neurohormonal activation (renin-angiotensin-aldosterone system, sympathetic system, cytokine release), which, although beneficial in acute cases, is responsible for a gradual deterioration in myocardial function. For instance, in response to a decrease in cardiac output, an increase in circulating norepinephrine (NE) can be seen, which acts on the sympathetic myocardial receptors—particularly beta-1—thus increasing myocardial contractility. In addition, by stimulating peripheral alpha receptors, NE induces peripheral vasoconstriction, which helps maintain blood pressure (Figure 1). This effect is counterbalanced by peripheral beta-2 stimula-
tion, and consequent vasodilation. Prolonged exposure of the heart to alpha- and beta-receptor stimulation unfortunately promotes left ventricular modeling, cell death due to necrosis or apoptosis, and water/salt retention.\textsuperscript{2}

The roles played by beta-1 and beta-2 myocardial receptors in cardiovascular homeostasis differ in normal and heart failure patients. In normal cases, there is little expression of beta-2 receptors at the myocardium, but they retain their full importance peripherally where they mediate vasodilation. In heart failure, however, beta-2 receptors can represent up to 40\% of total adrenergic receptors, because of the greatly diminished density of beta-1 receptors (down-regulation).\textsuperscript{3} There have been recent reports of the presence of beta-3 receptors, responsible for a negatively inotropic effect, and their density would appear to increase in heart failure.\textsuperscript{4} Currently, no specific treatment involving these receptors is available.

Finally, an inter-relationship also exists between the sympathetic and renin-angiotensin-aldosterone systems. Activation of the sympathetic system stimulates the release of renin, and thus angiotensin 2. This accentuates left ventricular remodeling and peripheral vasodilation, aggravating the heart failure.

Studies

Initial trials conducted in the late 1980s were small, and not designed to study total mortality. For example, the Metoprolol in Dilated Cardiomyopathy (MDC) study covered 383 patients,\textsuperscript{5} and the Cardiac Insufficiency Bisoprolol Study I (CIBIS I) had 681 patients.\textsuperscript{6} Both studies showed an improvement in ventricular function and morbidity, but results were not significant with respect to mortality. More recently, four large-scale multicenter randomized studies (Table 1) convincingly demonstrated the efficacy of beta-blockers in improving the survival of functional class II, III and IV heart failure patients.\textsuperscript{7-10} The drugs used in these studies were metoprolol, bisoprolol and carvedilol.

A significant decrease ranging from 34\% to 65\% in the relative risk of mortality was documented. The hospitalization rate for heart failure also was significantly reduced. Results were, however, equivocal with respect to bucindolol (not available in Canada).\textsuperscript{11} The majority of patients in these four studies were class II or III.

The only study to include class IV patients exclusively was the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial.\textsuperscript{10} The trial showed a 35\% reduction in the relative risk of mortality in 2,200 patients. More recently, the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) study examined carvedilol in a group of symptomatic and non-symptomatic post-infarction patients with a lowered ejection fraction.\textsuperscript{12} Once again, beneficial effects were confirmed, extending expected benefits to cover class I patients.

It is remarkable to think that these results occurred when more than 90\% of patients were already receiving ACE inhibitors. It should be remembered that ACE inhibitors reduce total mortality by some 20\% to 25\%, meaning that approximately 75 patients had to be treated...
annually for every life saved. This is compared with an average decrease in total mortality of 30% to 35% with beta-blockers (or the equivalent of 20 patients treated annually for every life saved).¹³

Different Types of Beta Blockers Studied

Not all beta-blockers available are appropriate for the treatment of cardiac insufficiency. For example, d-sotalol (additional anti-arrhythmia activity) increased mortality rates in the Survival with Oral d-sotalol (SWORD) study,¹⁴ possibly through pro-arrhythmia. Xamoterol (additional intrinsic sympathomimetic activity) also had a negative effect as far as the mortality rates of heart failure patients were concerned.¹⁵ This raised the possibility that the properties of the individual beta-blockers give different clinical results (Table 2).

One of the beta-blockers that improved survival rates in cardiac insufficiency, carvedilol, has no selective beta-1 properties, but it, nonetheless, presents an affinity for this receptor, which is 12 times greater than that of metoprolol. Carvedilol also blocks beta-2 and alpha-1 receptors, and has a potent antioxidant effect.¹⁶ Theoretically, therefore, it could block the remodeling and cytotoxic/hemodynamic effects induced by NE more fully.

The literature, however, shows the greater part of the negative effect of sympathetic activation is

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>NYHA Class</th>
<th>Avg. EF (%)</th>
<th>Avg. dose (mg)</th>
<th>Mortality placebo (%)</th>
<th>Mortality active treatment (%)</th>
<th>RR (%)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S. Carvedilol (Carvedilol)</td>
<td>1,094</td>
<td>2,3,4</td>
<td>22</td>
<td>45</td>
<td>7.8</td>
<td>3.2</td>
<td>65</td>
<td>21</td>
</tr>
<tr>
<td>CIBIS-II (Bisoprolol)</td>
<td>2,647</td>
<td>3,4</td>
<td>27</td>
<td>40% = 10</td>
<td>11% = 7.5</td>
<td>13% = 5</td>
<td>17.3</td>
<td>11.8</td>
</tr>
<tr>
<td>MERIT-HF (Metoprolol CR/XL)</td>
<td>3,991</td>
<td>2,3,4</td>
<td>28</td>
<td>159</td>
<td>11</td>
<td>7.2</td>
<td>38</td>
<td>26</td>
</tr>
<tr>
<td>BEST (Bucindolol)</td>
<td>2,695</td>
<td>3,4</td>
<td>23</td>
<td>—</td>
<td>33</td>
<td>30.2</td>
<td>5.7</td>
<td>—</td>
</tr>
<tr>
<td>COPERNICUS (Carvedilol)</td>
<td>2,200</td>
<td>4</td>
<td>≤ 25</td>
<td>74% = 25 (bid)</td>
<td>18.5</td>
<td>11.4</td>
<td>35</td>
<td>14</td>
</tr>
</tbody>
</table>

N = Number of patients; NYHA = New York Heart Association; EF = Ejection fraction; RR = Reduction in risk; NNT = Number of patients needed to treat; CIBIS-II = The Cardiac Insufficiency Bisoprolol Study II; MERIT-HF = Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; BEST = Beta-blockers Evaluation Survival Trial; COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival Trial
mediated by activation of the beta-1 receptor.\textsuperscript{16} The positive results of the CIBIS-II\textsuperscript{17} and Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF)\textsuperscript{8} studies appear to confirm this. Unlike carvedilol, bisoprolol and metoprolol also have the effect of re-establishing the activity of beta-1 receptors (up-regulation), resulting in greater cardiac sensitivity to NE.\textsuperscript{2} This could help re-establish myocardial contractility, but may equally aggravate NE toxicity. It is still not clear, therefore, whether the difference in carvedilol properties on the one hand, and those of metoprolol and bisoprolol on the other, are significant in a practice setting.

Recently, a randomized study compared metoprolol and carvedilol in congestive heart failure patients to quantify the differential effects of these drugs.\textsuperscript{18} The study documented a greater improvement in maximum exercise capacity with metoprolol, which could possibly be explained by a less depressed heart rate upon exertion. Carvedilol caused a greater improvement in left ventricular function, possibly because of more complete blockage of sympathetic receptors. On the other hand, patients’ symptoms, perception of quality of life, and tolerance of submaximal effort were identical in both groups.

While awaiting a direct comparison of mortality from the Carvedilol or Metoprolol European Trial (COMET) study, we must concluded that all three agents have proved useful in class II and III heart failure patients, but only carvedilol is appropriate in class IV patients.

**Use in Practice**

Current recommendations are to consider the addition of a beta-blocker in the case of patients presenting with functional class II or III congestive heart failure if caused by systolic dysfunction.\textsuperscript{19} This does not apply when classic beta-blocker contraindications are present (i.e., asthma, atrioventricular block, symptomatic bradycardia, diabetes with frequent hypoglycemia). This does not apply either in patients hospitalized for acute decompensation who require intravenous diuretics or intravenous inotropic support. Usually, diuretics and ACE inhibitors are started during hospitalization for decompensation, and beta-blockers are started later. In

### Table 2

Properties of Beta-blockers Used In Cardiac Insufficiency

<table>
<thead>
<tr>
<th>Agents</th>
<th>B1/B2 selectivity</th>
<th>a1 blocker</th>
<th>Vasodilation</th>
<th>Other properties</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol</td>
<td>No</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>12.5-100 bid</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>++</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>12.5-10 qid</td>
</tr>
<tr>
<td>Bucindolol</td>
<td>No</td>
<td>—</td>
<td>+</td>
<td>—</td>
<td>3-100 bid</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>No</td>
<td>Yes</td>
<td>+ (via a1)</td>
<td>Antioxidant</td>
<td>3.125-25 bid</td>
</tr>
</tbody>
</table>
Highly fragile patients, treatment should begin ideally in a heart failure clinic, but, in most cases, patients can be safely treated in an outpatient environment, providing certain rules are respected.

First of all, treatment should be started at extremely low doses: carvedilol, 3.125 mg twice daily (bid); bisoprolol, 1.25 mg daily (od); or metoprolol 12.5 mg bid. This dosage should be maintained for at least two to four weeks, and is doubled only if the patient has tolerated it well, aiming for the maximum dosage studied (Table 1). If the patient does not tolerate the increased dosage, the medication should not be considered a failure and treatment should be maintained at the tolerated dose. Significant benefits are already felt at the low dose, as shown in the Multicenter Oral Carvedilol Heart Failure Assessment (MOCHA) study, and with a number of beta-blockers in an Ontario-based observation study. Patients starting treatment must always be advised that all beta-blockers can cause a temporary deterioration in symptoms for a week or two, as well as dizziness and hypotension (particularly with carvedilol, because of its more complete sympathetic blockade). The patient’s diuretic dosage must be properly adjusted, up or down as required, without hesitation. The physician should confirm the disappearance of any side effects before considering an increase in the patient’s dosage.

If the above steps are taken, most patients will be able to tolerate high doses of beta-blockers. In practice, patients often see a subjective improvement in their condition, but there will also be benefits in terms of reduced hospitalization and mortality, even if there is no subjective improvement.

Many patients will obviously have to be rehospitalized at some point for clinical decompensation. Depending on the individual case, the beta-blockers can be continued by simply increasing diuretic dosage, or be decreased temporarily. In rare cases, they will have to be stopped completely. In such cases, every effort should be made to try to reintroduce them gradually.

Class IV patients form a specific group for whom carvedilol is now appropriate, based on the COPERNICUS study. Treatment should not be instituted, however, in the acute phase and, given the fragility of these patients, introduction of the treatment should be left to specialists.
Finally, while still awaiting the results of direct comparative studies, the choice of a specific beta-blocker will depend on the attending physician’s preference and the patient’s specific profile, except in the case of class IV patients.

Conclusion

Beta-blockers, which used to be contraindicated in heart failure, now form part of the standard therapeutic armamentarium and even represent the best approach in terms of absolute value. This new indication for one of the oldest classes of cardiovascular drugs represents a major change in our understanding and treatment of the cardiac insufficiency syndrome.

References