The medical treatment of chronic heart failure has undergone a remarkable transition in the past 10 years. The approach has changed from a short-term hemodynamic/pharmacological paradigm to a more long-term, reparative strategy that aims to favorably alter the biological properties of the failing heart. This is dramatically illustrated by the recent success in treating mild-to-moderate chronic heart failure with β-adrenergic blocking agents. This review describes how a treatment that began as a contraindication became an established treatment of chronic heart failure.

Rationale for β-Blocker Therapy in Chronic Heart Failure: Maladaptive Adrenergic Signaling and Altered but Persistent Signal Transduction in the Failing Heart

The failing human heart is adrenergically activated, which helps to maintain cardiac performance over the short term by increasing contractility and heart rate. In contrast, in the resting state there is no adrenergic support of normally functioning human left ventricles. Multiple lines of evidence indicate that it is the increase in cardiac adrenergic drive rather than an increase in circulating norepinephrine that is both initially supportive and then ultimately damaging to the failing human heart.

As shown in Table 1, there are 3 adrenergic receptors (β₁, β₂, and α₁) in human cardiac myocytes coupled to a positive inotropic response and cell growth. β₁-Adrenergic receptors are coupled via the “stimulatory” G protein Gₛ to the effector enzyme adenyl cyclase, which converts the substrate MgATP to cAMP. cAMP is a positively inotropic and chronotropic second messenger and is strongly growth promoting. In nonfailing human left or right ventricles, the β₁/β₂ ratio is 70 to 80/30 to 20, but in failing human ventricles, 35% to 40% of the total number of β-receptors are β₂ because of selective downregulation in the β₂ subtype. α₁ receptors are coupled via a different G protein (Gₐ) to the effector enzyme phospholipase C, which, through the second messenger diacyl glycerol, activates the growth-promoting protein kinase C family. Because α₁-receptors are upregulated in the failing heart, the cardiac myocyte adrenergic receptor profile changes from predominately (>70% of the total adrenergic receptor population) β₁ to more of a mixed 2:1:1 ratio in end-stage heart failure. β₂ Receptors are also present on adrenergic nerve terminals in the heart, where they facilitate norepinephrine release. The β₁-receptor may also be present in the human heart as a counterregulatory receptor coupled to the “inhibitory” G protein Gᵢ, and there is evidence for a “β₄” receptor.

Norepinephrine is an exceptionally cardiotoxic substance that produces cardiac myocyte injury in concentrations found in the failing human heart. Norepinephrine is mildly (10- to 30-fold compared with the binding affinity to β₂ receptors) β₁-receptor selective, and its cytotoxicity appears to be mediated through β₁ rather than α-adrenergic receptors. In transgenic mice, cardiac overexpression of human β₁ receptors or Gₛ or Gᵢ produces an overtly cardiomyopathic phenotype and ultimately chamber dilatation and systolic dysfunction. Overexpression of Gᵢ is also associated with increased markers of apoptosis, which can be produced in adult rat cardiac myocytes by β₁-agonist exposure. In adult rat myocytes, the β₁ receptor mediates apoptotic signaling, whereas the β₂ receptor is antiapoptotic via coupling to the inhibitor and G protein (Gi). High levels of cardiac overexpression of the human β₂ receptor eventually result in depressed systolic function and a cardiomyopathy phenotype, and cardiac expression of a constitutively activated α₁ receptor produces concentric hypertrophy. These data from model systems incontrovertibly indicate that chronic adrenergic signaling is a harmful compensatory mechanism in the failing human heart. The data are extremely convincing for chronic β₁-receptor signaling and less convincing, but likely, for chronic β₂- and α₁-receptor pathway activation.

In the failing heart, β-adrenergic signal transduction is reduced secondary to desensitization changes in β₁ and β₂ receptors, the inhibitory G protein (Gᵢ), an enzyme responsible for modulating receptor activity by phosphorylation (βARK), and even in the expression of the adenyl cyclase enzyme itself. In end-stage failing heart, 50% to 60% of the total signal transducing potential is lost, but substantial signaling capacity remains. These and other data from model systems suggest that the β-adrenergic receptor pathway desensitization changes present in the failing human heart are adaptive changes, and that a potentially effective therapeutic strategy would be to add to this endogenous antiadrenergic strategy by inhibiting receptor signal transduction.

Thus, the continuously increased adrenergic drive present in the failing human heart delivers adverse biological signals...
TABLE 2. Biological Responses Mediated by Adrenergic Receptors in the Human Heart

<table>
<thead>
<tr>
<th>Biological Response</th>
<th>Adrenergic Receptor Mediation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac myocyte growth</td>
<td>$\beta_1$, $\beta_2$, $\alpha_1$</td>
</tr>
<tr>
<td>Positive inotropic response</td>
<td>$\beta_1$, $\beta_2$, $\alpha_1$ (minimal)</td>
</tr>
<tr>
<td>Positive chronotropic response</td>
<td>$\beta_1$, $\beta_2$</td>
</tr>
<tr>
<td>Myocyte toxicity</td>
<td>$\beta_1$, $\beta_2$, $\beta_3$ (? $&lt; \beta_2$)</td>
</tr>
<tr>
<td>Myocyte apoptosis</td>
<td>$\beta_1$</td>
</tr>
</tbody>
</table>

to the cardiac myocyte via $\beta_2$ and likely $\beta_2$ and $\alpha_1$-adrenergic receptors. This is the fundamental basis for the use of antiadrenergic agents in the treatment of chronic heart failure.

Three Classes of $\beta$-Blockers Available for Clinical Use

There are now 3 classes of $\beta$-blockers available for clinical use. Table 2 gives the adrenergic receptor blocking profiles for selected $\beta$-blocking agents, including those that have been widely used in heart failure clinical trials. Propranolol is the prototype nonselective compound, introduced into clinical practice in 1968 as an antianginal agent. Propranolol and other “first-generation” compounds, such as timolol, are nonselective agents with equal affinities for blocking $\beta_1$ and $\beta_2$ receptors and no important pharmacological properties other than $\beta$-blockade.

In the 1970s, pharmaceutical companies developed “cardioselective” or second-generation $\beta$-blockers that selectively antagonized $\beta_1$ compared with $\beta_2$-receptors. This was done in the mistaken belief\(^{10,11}\) that the human heart could be selectively $\beta$-blocked, on the basis of data from animal models in which only $\beta_1$-receptor–mediated responses were identified in the myocardium. It was hoped that a lack of $\beta_2$-receptor blockade would also reduce some of the perceived peripheral and pulmonary side effects of $\beta$-blockers, a hypothesis that also was never conclusively proved. The first truly selective $\beta_2$-blocking agent was practolol,\(^{31}\) which was sufficiently $\beta_1$-selective that it could be used along with propranolol to demonstrate 3 distinct subtypes ($\beta_1$, $\beta_2$, and $\beta_3$) of $\beta$-adrenergic receptors,\(^{32}\) which were ultimately shown to be the products of 3 distinct genes.\(^{33–35}\) Practolol was also the first $\beta$-blocking agent to be therapeutically administered by the pioneering Goteborg group to a patient with chronic heart failure.\(^{36}\) Ultimately, practolol was removed from clinical practice because of immunological adverse effects and was replaced by metoprolol in the Goteborg studies. As shown in Table 2, metoprolol is approximately 75-fold selective for human $\beta_1$ versus $\beta_2$-receptors. In the 1980s, pharmaceutical companies developed even more $\beta_1$-selective compounds, such as bisoprolol, which is 238-fold selective (Table 2).

As discussed below, both metoprolol and bisoprolol have been used extensively in heart failure trials and both have recently been shown to reduce mortality in phase 3 clinical trials.\(^{37,38}\)

In the 1970s and 1980s, another drug development effort aimed at improving the treatment of hypertension led to the creation of $\beta$-blockers with vasodilating activity. These “third-generation” compounds were designed to treat hyper-

---

TABLE 2. Adrenergic Receptor Blocking Affinities of $\beta$-Blocking Agents in Human Receptors

<table>
<thead>
<tr>
<th>Generation/Class</th>
<th>Compound</th>
<th>$K(\beta_1)$, nmol/L</th>
<th>$K(\beta_2)$, nmol/L</th>
<th>$\beta_1/\beta_2$ Selectivity</th>
<th>$K(\alpha_1)$, nmol/L</th>
<th>$\beta_1/\alpha_1$ Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>First/nonselective</td>
<td>Propranolol</td>
<td>4.1</td>
<td>8.5</td>
<td>2.1</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Second/selective $\beta_1$</td>
<td>Metoprolol</td>
<td>45</td>
<td>3345</td>
<td>74</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>Bisoprolol</td>
<td>121</td>
<td>14 390</td>
<td>119</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Third/$\beta$-blocker–vasodilator</td>
<td>Carvedilol</td>
<td>4.0</td>
<td>29</td>
<td>7.3</td>
<td>9.4</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td>Bucindolol</td>
<td>3.6</td>
<td>5.0</td>
<td>1.4</td>
<td>238</td>
<td>66 (19)*</td>
</tr>
<tr>
<td></td>
<td>Nebivolol</td>
<td>5.8</td>
<td>1700</td>
<td>293</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

$\beta$-Receptors are the average of data from radioligand binding data in myocardial membranes and recombinant receptors, and inhibition in functional assays; $\alpha_1$-receptors are from myocardial membranes. Metaprolol and bisoprolol data are from radioligand binding data in myocardial membranes. Nebivolol data are from another laboratory in guinea pig receptor preparations.\(^{43}\)

$K(\beta_1)$ is the average high-affinity dissociation constant determined from $^{125}$ICYP competition curves in human ventricular myocardial membranes, dissociation constant determined from competition curves in transfected cells expressing recombinant human $\beta_1$ receptors, and dissociation constant determined from inhibition of isoproterenol-mediated stimulation of muscle contraction in preparations of nonfailing human heart. $K(\beta_2)$ is the average low-affinity dissociation constant determined from $^{125}$ICYP competition curves, dissociation constant determined from simple curve fitting in transfected cells expressing recombinant human $\beta_2$ receptors, and dissociation constant determined from inhibition of isoproterenol-mediated stimulation of adenylyl cyclase in membrane preparations of human heart. $K(\alpha_1)$ is the dissociation constant determined from $^{125}$IBE2254 competition curves in human ventricular myocardial membranes.

*Based on an $\alpha_1$, $K$ of 69 nmol/L in human saphenous vein ring segments (RL Tackett, personal communication, 1999).
tension, and the prototype agent is labetalol. Labetalol is an α-, β-blocking agent with a higher affinity for α₁- than β₁- or β₂-receptors. Labetalol has not been systematically investigated in heart failure populations but has been shown to improve myocardial function in subjects with hypertensive cardiomyopathy. Another third-generation compound with limited but favorable experience in heart failure trials is nebivolol, which is a markedly β₁-selective compound whose vasodilatory action appears to be due to potentiation of nitric oxide. Two other β-blockers with vasodilating activity, carvedilol and bucindolol, have been extensively evaluated in the treatment of chronic heart failure.

As shown in Table 2, carvedilol is a slightly (≈7-fold) β₁-selective agent that becomes nonselective at higher target doses. Carvedilol is also a potent α₁-blocking agent, with ≈2- to 3-fold selectivity for β₁- versus α₁-receptors (Table 2). This degree of α₁-blockade is responsible for the moderate vasodilator properties of carvedilol.

Bucindolol is a completely nonselective β-blocking agent with mild vasodilator properties that were originally thought not to be due to α₁-blockade in view of the 60- to 70-fold difference in binding affinity between human myocardial β₁- or β₂- and α₁-receptors as deduced from radioligand competition curves (Table 2). However, recent data in isolated human saphenous vein preparations indicate that bucindolol can antagonize α₁-mediated vasoconstrictor responses at concentrations achieved after oral dosing (R.L. Takett, personal communication, 1999; Table 2), and α₁-blockade is the only specific vasodilator mechanism that has been identified in animal systems.

Thus, it is likely that the weak vasodilator properties of bucindolol are due to α₁-adrenergic receptor blockade. As with other β-blocking agents that improve ventricular function in chronic heart failure, bucindolol has no intrinsic sympathomimetic activity in human myocardium. Compared with other β-blocking agents that have been widely used in chronic heart failure, bucindolol possesses the lowest amount of "inverse agonism," or the ability of an antagonist to inactivate active-state receptors. This seems to correlate with a low incidence of symptomatic bradycardia with bucindolol, despite the fact that it reduces average heart rate to the same extent as target doses of metoprolol and carvedilol. This same low inverse agonist profile may contribute to the apparent low amount of myocardial depression on acute administration of bucindolol.

Because they (1) block both β₁- and β₂-adrenergic receptors, (2) reduce cardiac and/or systemic adrenergic drive, (3) do not upregulate downregulated β₁-adrenergic receptors, and (4) block α₁-receptors, the third-generation compounds carvedilol and bucindolol provide a more comprehensive antiadrenergic effect than do second-generation, β₁-selective compounds. Limited data suggest that compared with second-generation compounds, third-generation compounds produce more beneficial effects on left ventricular function. However, some data also demonstrate no difference between a second- and third-generation compound. Both second- and third-generation compounds improve intrinsic systolic function, and prevent deterioration in function and progression in remodeling. As discussed below, from a clinical standpoint it would appear that both second- and third-generation compounds reduce hospitalizations and mortality, but quantitative differences in clinical responses may exist. On the other hand, because chronic β₁-adrenergic receptor signaling may be the dominant cardiotoxic pathway in the failing heart, β₁-selective agents may be as or even more efficacious than pan-adrenergic receptor blocking third-generation compounds. The issue of whether second- and third-generation compounds provide differences in clinical efficacy can be determined only by direct comparison trials, such as the Carvedilol or Metoprolol European Trial (COMET), which is assessing the effects of carvedilol versus metoprolol on all-cause mortality.

Effects on Initiation of Therapy
Because the failing heart is dependent on adrenergic support, the administration of any β-blocking agent to a subject with overt heart failure from systolic dysfunction will cause some degree of myocardial depression that will be clinically manifest to various degrees. Acute administration of first-generation compounds, such as propranolol, causes a decrease in contractile state. This, plus a concomitant increase in systemic vascular resistance, leads to a profound decrease in cardiac output, which results in a drug intolerance rate of >20%.

On the other hand, second-generation, β₁-selective compounds can be administered in low starting doses to subjects with mild to moderate heart failure and moderate to severe left ventricular dysfunction. The reason is that β₁-receptor blockade leaves the β₂-receptor unblocked and capable of supporting myocardial function, either directly or through increased norepinephrine overflow mediated by presynaptic β₂-receptors. Additionally, there is less reflex vasoconstriction with β₁-selective agents because unblocked peripheral vascular β₂-receptors can mediate vasodilatation. The overall effect is that cardiac output and organ perfusion are reduced to a lesser extent than with first-generation compounds. The drug tolerability rates for the second-generation compound metoprolol in clinical trials, with challenges of 5 or 6.25 mg BID, range from 79% to 100%

The third-generation compounds carvedilol, bucindolol, and nebivolol have the advantage of afterload reduction to counteract the negative inotropic properties of adrenergic withdrawal. As a result, in grouped data bucindolol does not lower cardiac output, and carvedilol may even increase it slightly. Because of stereoselective hepatic metabolism of the S isomer and stereospecificity of the S isomer for binding to β- but not α-adrenergic receptors, on oral administration the α-blocking effects of carvedilol are observed to about the same degree as the β-blocking effects. In contrast, on intravenous administration, the β-blocking effects of carvedilol predominate (A. Lahiri, personal communication, 1998). The prominent vasodilator action of orally administered carvedilol leads to frequent orthostatic symptoms on initiation of therapy or uptitration, most of which are self-limiting or can be managed by smaller diuretic doses. Orthostatic symptoms do not typically occur with bucindolol because it is only a mild vasodilator.
Carvedilol is tolerated by ~92% of subjects with mild to moderate heart failure challenged with 3.125 to 6.25 mg BID, whereas bucindolol is tolerated by ~98% of mild to moderate heart failure subjects challenged with 6.25 to 12.5 mg BID.53

The vasodilator properties of third-generation agents allow those compounds with a nonselective profile to be administered with an acceptable tolerability rate, which in effect allows for administration of agents with a more comprehensive antiadrenergic profile.53,57 However, it is unclear whether vasodilation contributes to the long-term benefit of third-generation compounds because after long-term therapy with carvedilol, the reduction in systemic vascular resistance is not different from placebo- or metoprolol-treated control populations.47,56

### Effects of Long-Term Treatment on Myocardial Function and Chamber Characteristics

The myocardial effects of long-term treatment with β-blocking agents have been recently reviewed in detail.1,53,57,76 The striking generalization about the long-term effects of β-blockade on myocardial function is that they are diametrically opposite to the short-term negative inotropic effects.1 That is, every placebo-controlled trial conducted for ≥3 months of treatment has demonstrated improved systolic function compared with the second-generation compound bisoprolol, subjects with symptomatic heart failure from idiopathic cardiomyopathy/systolic dysfunction phenotype, they would be expected to produce favorable effects on the natural history of heart failure, which appears to be the case. For example, the third-generation agent carvedilol improves systolic function in a dose-related manner when administered to chronic heart failure subjects over a 6.5-month period, and these effects are associated with an almost mirror image dose-related reduction in mortality.77 Additionally, in studies with the second-generation compound bisoprolol, subjects who demonstrated an improvement in systolic function had a mortality benefit compared with placebo and compared with the small number of subjects whose left ventricular function deteriorated on bisoprolol.62

### Effects of Long-Term Treatment on Clinical End Points

This discussion of the effects of β-blocking agents on clinical end points will be confined to placebo-controlled trials that enrolled ≥100 patients with a minimum follow-up of 3 months. The only compound in clinical development that is not discussed is nebivolol, which has not yet begun phase 3 trials. All the discussed trials were conducted since 1985, with background therapy of diuretics, digoxin, and ACE inhibitors.

### Metoprolol

The first placebo-controlled multicenter trial with a β-blocking agent was the Metoprolol in Dilated Cardiomyopathy (MDC) trial,78 planned in 1982 to 1983 and conducted in European and US centers between 1985 and 1991 (Table 3). This trial compared metoprolol tartrate to placebo in subjects with symptomatic heart failure from idiopathic...
dilated cardiomyopathy. The trial was powered on an expected 50% reduction by metoprolol in the combined end point of all-cause mortality and deterioration of the patient to the point of requiring listing for heart transplantation. MDC also had numerous prespecified secondary end points, which included mortality alone, hospitalizations, left ventricular function, quality of life, and exercise tolerance.\textsuperscript{78} In the MDC trial, metoprolol at an average dose of 108 mg/d reduced the prevalence of the primary end point by 34%, which was not quite statistically significant ($P=0.058$).\textsuperscript{78} The benefit was entirely due to a reduction by metoprolol in the morbidity end point (a reduction by metoprolol of 90%), inasmuch as all-cause mortality actually trended greater in the metoprolol-treated group.\textsuperscript{78} In addition, metoprolol compared with placebo improved left ventricular function, quality of life, hospitalizations, and exercise tolerance at 12 months.\textsuperscript{78}

The results of the MDC trial were viewed as nondefinitive but quite promising, and they led to a more traditional placebo-controlled mortality trial (Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure [MERIT-HF], Table 3), which began enrolling subjects in early 1997 and was stopped prematurely for a 34% reduction in mortality in the metoprolol arm.\textsuperscript{38} The MERIT-HF trial enrolled 3991 subjects with ischemic and nonischemic dilated cardiomyopathies who had class II through IV heart failure;\textsuperscript{38} the metoprolol preparation used was a continuous release formulation.\textsuperscript{38} The third-generation nonselective compound bucindolol was the first $\beta$-blocking agent shown to improve left ventricular function in a placebo-controlled trial.\textsuperscript{51} In that trial, this nonselective vasodilating compound was well tolerated,\textsuperscript{51} in marked contrast to previous experiences\textsuperscript{2,3} and subsequent experiences with the nonselective first-generation agent propranolol. The second multicenter trial performed with a $\beta$-blocking agent was the bucindolol multicenter trial,\textsuperscript{81} which was a phase 2 dose-response trial designed to select a dose of bucindolol to be used in phase 3 trials (Table 3). This trial had primary end points of left ventricular function and exercise tolerance, with secondary end points of quality of life and mortality.\textsuperscript{81} In this multicenter trial conducted in symptomatic ischemic and nonischemic cardiomyopathy patients over a 12-week period, bucindolol produced a dose-related improvement in left ventricular function and a strong trend toward a reduction in end-systolic and end-diastolic volumes, along with a dose-

<table>
<thead>
<tr>
<th>Trial</th>
<th>Agent</th>
<th>Primary End Point</th>
<th>Sample size, n</th>
<th>Population</th>
<th>Status December 1999</th>
</tr>
</thead>
<tbody>
<tr>
<td>BEST</td>
<td>Bucindolol</td>
<td>Mortality</td>
<td>2708</td>
<td>NYHA III–IV</td>
<td>Ended July 1999</td>
</tr>
<tr>
<td>COPERNICUS</td>
<td>Carvedilol</td>
<td>Mortality</td>
<td>1800</td>
<td>NYHA III–IV</td>
<td>Enrolling</td>
</tr>
<tr>
<td>COMET</td>
<td>Metoprolol, Carvedilol</td>
<td>Mortality</td>
<td>4000</td>
<td>NYHA II–IV</td>
<td>Enrollment complete</td>
</tr>
<tr>
<td>CHRISTMAS</td>
<td>Carvedilol</td>
<td>Hibernating myocardium</td>
<td>400</td>
<td>Ischemic CMY</td>
<td>Enrollment complete</td>
</tr>
<tr>
<td>CARMEN</td>
<td>Carvedilol</td>
<td>Remodeling</td>
<td>400</td>
<td>NYHA I–II</td>
<td>Enrolling</td>
</tr>
<tr>
<td>EMPOWER</td>
<td>Enox + Metoprolol</td>
<td>M + M</td>
<td>400</td>
<td>NYHA III–IV</td>
<td>Starting early 2000</td>
</tr>
</tbody>
</table>

| Metop indicates metoprolol; Enox, enoximone; M+M, mortality and morbidity; CMY, cardiomyopathy; and IIIb, intolerant of $\beta$-blockers alone. |
unrelated prevention of deterioration in left ventricular function. Bucindolol did not affect quality of life or exercise tolerance, although there was a trend for improved submaximal exercise. From the results of this trial, the high dose (200 mg/d) of bucindolol was selected for the target dose in subjects weighing ≥75 kg in the phase 3 bucindolol trials. The largest of these phase 3 trials, the β-Blocker Evaluation of Survival Trial (BEST), was recently completed, with 2708 subjects with advanced (class III and IV) heart failure randomized to placebo or bucindolol (Table 4). In BEST, bucindolol produced a nonsignificant (P=0.10) 10% reduction in total mortality, with favorable effects on most secondary end points (E. Eichhorn, personal communication, 1999). The effect on mortality in BEST was less than that observed in MERIT-HF80 or CIBIS-II.37 This suggests that patients with more advanced heart failure respond less well to β-blockade than do subjects with mild-to-moderate heart failure, or that bucindolol is less efficacious than metoprolol or bisoprolol.

Bisoprolol
The third multicenter trial planned and performed was the Cardiac Insufficiency Bisoprolol Study (CIBIS-I; Table 3), which was a placebo-controlled trial of the effects of bisoprolol on mortality in symptomatic ischemic or nonischemic cardiomyopathy subjects treated for an average follow-up of 22.8 months.83 This trial, powered on an unrealistically high expected event rate in the control group, ended up with a statistically insignificant 20% mortality reduction.83 In addition, the benefit in this trial was confined to subjects with nonischemic cardiomyopathy who, compared with those receiving placebo, had a 47% reduction (P=0.01) in mortality.83 Despite the lack of overall statistical significance in the CIBIS-I trial, the reduction in mortality was similar to that accomplished with ACE inhibitors and was viewed as encouraging. This prompted a follow-up trial, CIBIS-II,37 with more conservative effect size estimates and sample size calculations.

The CIBIS-II trial was stopped by the Data and Safety Monitoring Committee 18 months early because of a 32% reduction (P<0.001) in all-cause mortality (Table 4) in the bisoprolol-treated group.37 CIBIS-II enrolled 2647 patients with class III or IV heart failure from ischemic and nonischemic cardiomyopathies, with a median follow-up of 1.3 years.37 In addition to the reduction in mortality, bisoprolol also reduced hospitalizations (by 20%) and cardiovascular deaths (by 29%). In CIBIS-II,37 deaths classified as sudden were statistically reduced (by 44%) in the bisoprolol group, whereas pump failure deaths were nonsignificantly reduced by 26%. This trend in a greater reduction in sudden versus pump failure deaths was opposite to that obtained in CIBIS-I,83 in which bisoprolol reduced pump failure deaths by 48% and sudden ventricular tachycardia/fibrillation deaths by 21%. Another difference between CIBIS-I and CIBIS-II was the effect on ischemic versus nonischemic cardiomyopathy, which also demonstrated opposite trends. In CIBIS-I,83 the reduction in mortality in the nonischemic group was by 47% (P=0.01), whereas in patients with a history of myocardial infarction, there was a trend to an increase in mortality (by 11%) in the bisoprolol group. One possible explanation for the differences between CIBIS-I and CIBIS-II is the average target doses of bisoprolol used: 10 mg/d in CIBIS-II37 and 5 mg/d in CIBIS-I.83

Although CIBIS-II enrolled subjects with class III (>90% of the total) or IV symptoms, the annualized placebo mortality was only 13.2%.37 This mortality rate is similar to the enalapril arm of the Studies of Left Ventricular Dysfunction (SOLVD) treatment trial,84 which comprised 68% class I and II patients. Additionally, the average blood pressure of subjects enrolled in CIBIS-II was 130/80 mm Hg, which is higher than the blood pressures of the SOLVD patients84 or the subjects enrolled in the US carvedilol trials, in which ≈50% were class II or III.85 A relatively large proportion of CIBIS-II subjects were enrolled in eastern Europe and Russia, where practice patterns, heart failure origin, or symptom interpretation may not be comparable to western Europe and the United States. Nevertheless, the results of CIBIS-II were internally consistent through all major demographic groups,37 and the impressive results constitute a landmark clinical trial in the development of β-blockade as a treatment for chronic heart failure.

Carvedilol
Carvedilol is currently the only β-blocker approved for treatment of chronic heart failure in the United States and most other countries. There have been 1748 subjects enrolled in 8 randomized, placebo-controlled phase 2 and 3 clinical trials with carvedilol.77,85–93 In the United States, there were 2 medium-sized phase 3 trials designed to achieve Food and Drug Administration (FDA) approval for a heart failure indication, the Multicenter Oral Carvedilol in Heart Failure Assessment (MOCHA)77 and Prospective Randomized Evaluation of Carvedilol in Symptoms and Exercise (PRECISE)88 trials (Table 3). Because of the nature of the submaximal exercise primary end point, these trials were relatively short, consisting of 6 months of maintenance after an initial 2 to 4 weeks of uptitration.77,88 Two additional supportive trials were also conducted as part of the US carvedilol trials program, enrolling subjects who were “outliers” on baseline submaximal exercise testing.89–90 The Mild Heart Failure carvedilol study (Table 3)89 enrolled subjects who exercised >450 m on the 6-minute walk test, and the Severe Heart Failure carvedilol trial (Table 3)90 enrolled subjects who exercised <150 m on the 6-minute walk test, which was used to allocate subjects to each of the 4 US trials.77,88–90 These trials all had secondary clinical end points consisting of cardiovascular hospitalizations during the maintenance phase, symptom and quality of life assessments, and left ventricular function measured by radionuclide ventriculography.

The US carvedilol trials were stopped prematurely by the data and safety committee monitoring all 4 trials because of a highly significant (P<0.0001) reduction in mortality by carvedilol, 65% compared with placebo.83 The MOCHA77 and PRECISE88 trials were completed by the time the monitoring committee stopped the entire program, but the mild89 and severe90 trials were stopped prematurely. Neither MOCHA77 nor PRECISE88 demonstrated an improvement in their submaximal exercise primary end points by carvedilol,
but MOCHA did demonstrate a highly significant, dose-related reduction in mortality by 73%.77 Both MOCHA77 and PRECISE88 demonstrated a reduction in cardiovascular hospitalizations by carvedilol, and assessments of heart failure symptoms were improved in PRECISE.89 Despite not reaching completion, the mild trial demonstrated a significant improvement in the primary, “combined” end point of total mortality or cardiovascular hospitalizations or increasing heart failure medication.89 In the severe trial, there was no significant effect of carvedilol compared with placebo on the primary end point of the trial (quality of life), but global heart failure assessments improved in the carvedilol-treated patients.90 In all trials conducted in the United States and elsewhere,77,85–93 carvedilol improved left ventricular function. In MOCHA,77 the improvement was highly dose related, suggesting that the improvement in survival was related to improved ventricular function. Although carvedilol was generally well tolerated in the randomized subjects in these trials, 8.6% of enrolled subjects could not tolerate carvedilol on initial challenge, and these subjects were not randomized.85

The Australia-New Zealand trial had 2 phases, an initial 6-month submaximal exercise trial that showed no benefit by carvedilol (ANZ carvedilol I in Table 3)91 and a longer phase (ANZ carvedilol II in Table 3) that showed a reduction in the combined end point of mortality or cardiovascular hospitalizations.92 Additionally, when the US trials were analyzed retrospectively for this combined end point, all but the severe trial showed a reduction compared with placebo.94

The interpretation of the carvedilol US trials database generated much comment and discussion,95–97 including spirited debate at 2 FDA Cardiorenal Advisory Committee meetings. The main points of contention were the interpretation of the mortality data and the failure of 3 of the 4 US trials to meet their primary end points. Despite the high degree of statistical significance, the mortality data are not considered conclusive because of the short-term follow-up and the small total number of deaths,77,85 as well as the fact that all-cause mortality was not a prespecified primary or secondary efficacy end point in these trials. Ultimately, carvedilol was approved in early 1997 by the FDA for the indications of delaying the progression of the myocardial disease process and lowering the combined risk of morbidity plus mortality.98

The FDA decision was based on the facts that the mild heart failure trial90 met its primary end point of delaying the process of heart failure and that carvedilol reduced the secondary combined end point of mortality plus cardiovascular hospitalizations across all 4 US trials77,84–90 and the 1 conducted in Australia and New Zealand.92 Because the mortality effect of carvedilol and its efficacy in advanced heart failure have not been established, a mortality trial with carvedilol in advanced, class III to IV heart failure, Carvedilol Prospective Randomized Cumulative Survival Trial (COPERNICUS), is now being conducted (Table 4).

**General Interpretation of Clinical Results**

**With β-Blocking Agents**

The collective interpretation of the placebo-controlled β-blocker data generalized in subjects with mild-to-moderate heart failure is that the consistently demonstrated favorable effects on ventricular function and remodeling are, as expected,1,57 translated into clinical benefits. The clinical benefits include a decrease in mortality, a reduction in morbidity as assessed by hospitalization rate, and in some but not all trials, improved heart failure symptoms. Moreover, these favorable effects on the natural history of heart failure seem to be exerted across most demographic or descriptive groups, including ischemic versus nonischemic cause of dilated cardiomyopathy,37,38,77,78,85–93,99–101 older versus younger subjects,37,38,101 diabetic versus nondiabetic subjects,38,102 and lower versus higher initial ejection fractions.38,85 However, more data are needed to assess the effects of β-blockade in certain demographic groups, particularly women, subjects >75 years of age, and racial subsets. The latter issue may be particularly important. The BEST Trial in patients with advanced heart failure demonstrated a worse outcome in blacks versus nonblacks treated with β-blockade (E. Eichhorn, personal communication, 1999); however, in the carvedilol trials in the United States, black subjects with mild-to-moderate heart failure responded to carvedilol as well as did nonblack subjects.103

In addition to the favorable effects on myocardial function and structure, the general mechanisms through which β-blocking agents reduce mortality likely involve their established antiarrhythmic and anti-ischemic properties. In contrast to ACE inhibitors, β-blocking agents have consistently lowered the sudden death rate in heart failure trials,36,37,75,83 which suggests an antiarrhythmic contribution to mortality reduction. Because of the well-established “secondary prevention” database in ischemic heart disease, it is likely that anti-ischemic properties of β-blocking agents contribute to mortality reduction in subjects with heart failure from ischemic cardiomyopathy.

On the basis of the comparative effects on left ventricular function and remodeling1 and the additional mortality-lowering mechanisms possessed by β-blocking agents, it is not surprising that in established mild-to-moderate heart failure, β-blocking agents have generally had a quantitatively greater effect than ACE inhibitors on mortality reduction (Table 5). Table 5 lists all ACE inhibitor trials conducted in established LV dysfunction (excluding post-myocardial infarction trials) and symptomatic heart failure, and β-blocker trials conducted in mild-to-moderate heart failure. This comparison yields an identical annualized placebo mortality of 11% (Table 5). As shown in Table 5, the average reduction in mortality achieved by 12 months of treatment with an ACE inhibitor is 16%. Because β-blocker trials have been conducted on a background of ACE inhibition, the average reduction in mortality of 36% shown with β-blockade is additive with the ACE inhibitor data. By sequentially combining the average relative risks, the reduction in mortality by the combination of treatments is 46% (Table 5), which is obviously major progress in the treatment of chronic heart failure.

**Pharmacokinetic Issues**

The strategy for administering all β-blocking agents in the setting of chronic heart failure is to start at extremely low doses70 and increase the dose gradually, usually at weekly or biweekly intervals. With this strategy, target doses that can
substantially (by ≥20 bpm) decrease exercise heart rate can be achieved in most patients within 4 to 6 weeks of drug initiation. The pharmacological half-lives of metoprolol tartrate, carvedilol, and bucindolol dictate twice-daily dosing, whereas bisoprolol and metoprolol succinate CR can be given once daily. Carvedilol, metoprolol, bucindolol, and nebivolol are all highly lipophilic compounds that are extensively metabolized and cleared by the liver; bisoprolol is less lipophilic and exhibits mixed hepatic/renal clearance.106 First-pass hepatic metabolism occurs with all these agents, so the bioavailability is relatively low, ranging from 20% to 50%. However, when liver congestion and decreased liver function are present, such as in advanced heart failure, the bioavailability is relative low, ranging from 20% to 50%. However, when liver congestion and decreased liver function are present, such as in advanced heart failure, the bioavailability increases, and doses of lipophilic β-blockers produce relatively greater degrees of β-blockade. Thus, the doses of lipophilic β-blockers may have to be reduced in the presence of liver dysfunction, whereas the doses of bisoprolol may have to be reduced in the presence of either liver or renal dysfunction. Pharmacokinetic interaction with other heart failure medications, including warfarin, does not typically occur with β-blocking agents that are used in heart failure. Carvedilol increases the oral bioavailability of digoxin, but the increase in digoxin plasma level is small (10% to 15%).107

Lipophilic β-blocking agents are hepatically metabolized by cytochrome P450 2D6 (CYP2D6) oxidation. In subjects with polymorphic variants of CYP2D6 responsible for the debrisoquin “poor metabolizer” phenotype (present in 2% to 10% of US populations), the elimination half-life may be prolonged, and plasma levels and the degree of β-blockade may be increased.108 In addition, stereoselective metabolism by CYP2D6 occurs for some but not all lipophilic β-blockers. Carvedilol undergoes stereoselective metabolism of the S isomer as described earlier, which after oral administration leads to plasma concentrations of the R isomer that are 2- to 3-fold higher than the S isomer.45,73,106 In the poor metabolizer phenotype, the clearance of R carvedilol is further reduced relative to the S isomer.109 This would lead to a relatively greater degree of α- versus β-blockade in these individuals compared with subjects who are extensive metabolizers of debrisoquin. However, it is unclear whether this is of any clinical significance. Metoprolol also undergoes stereoselective metabolism by CYP2D6 but in favor of the R isomer.110 Stereoselective metabolism of metoprolol results in only a small difference in S/R plasma levels (1.35-fold higher S/R ratios in extensive debrisoquin metabolizers, reduced to an S/R ratio of 1 in poor metabolizers).110 However, in poor metabolizers taking metoprolol, the lower S/R ratio leads to less β-blockade relative to plasma levels,111 which tends to cancel the effect of the increased plasma levels of both isomers that is related to the lower oxidation rate. Clinically important stereoselective metabolism does not occur for bisoprolol,112 nebivolol,113 or bucindolol (D. Ward, personal communication, 1999).

Who Should Be Treated With a β-Blocking Agent?

Subjects with mild to moderate compensated heart failure from nonischemic or ischemic dilated cardiomyopathies with NYHA class II to III symptoms on standard treatment, including diuretics and ACE inhibitors, who do not have a contraindication to β-blockade are candidates for treatment with a β-blocking agent. Subjects who are treated with β-blocking agents should not have decompensated heart failure because the myocardial depression that accompanies

<table>
<thead>
<tr>
<th>Trial</th>
<th>Agent</th>
<th>NYHA Class</th>
<th>Subjects Enrolled, n</th>
<th>12-Month Placebo Mortality, %</th>
<th>12-Month Effect Size Decrease, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEIs CONSENSUS-I104</td>
<td>Enalapril</td>
<td>IV</td>
<td>253</td>
<td>52</td>
<td>31</td>
</tr>
<tr>
<td>SOLVD-Rx84</td>
<td>Enalapril</td>
<td>I–III</td>
<td>2569</td>
<td>15</td>
<td>21</td>
</tr>
<tr>
<td>SOLVD-Asx105</td>
<td>Enalapril</td>
<td>II</td>
<td>4228</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>I–IV</td>
<td>7050</td>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td>β-Blockers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIBIS-I83</td>
<td>Bisoprolol</td>
<td>III, IV</td>
<td>641</td>
<td>11</td>
<td>20</td>
</tr>
<tr>
<td>Carvedilol US85</td>
<td>Carvedilol</td>
<td>III, IV</td>
<td>1094</td>
<td>10</td>
<td>66</td>
</tr>
<tr>
<td>CIBIS-II87</td>
<td>Bisoprolol</td>
<td>III, IV</td>
<td>2647</td>
<td>13</td>
<td>33</td>
</tr>
<tr>
<td>MERIT-HF38</td>
<td>Metoprolol CR</td>
<td>II–IV</td>
<td>3991</td>
<td>11</td>
<td>35</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>II–IV</td>
<td>8373</td>
<td>11</td>
<td>36</td>
</tr>
<tr>
<td>Combined mortality reduction, ACEI + β-blockers</td>
<td></td>
<td></td>
<td>15423</td>
<td>11</td>
<td>46</td>
</tr>
<tr>
<td>Comparison, ACEI vs β-blockade</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class II–IV (SOLVD-Asx excluded)</td>
<td></td>
<td></td>
<td></td>
<td>P=0.006</td>
<td></td>
</tr>
</tbody>
</table>

SOLVD-Asx indicates SOLVD Asymptomatic LV Dysfunction Trial; ACEI, ACE inhibitor. *Twelve-month mortality rates taken from survival curves when data were not directly available in published material.
initiation of therapy can be life-threatening in such individuals. At present, the only FDA-approved agent is carvedilol, but metoprolol and bisoprolol are approved for other cardiovascular indications. For now, subjects with advanced class III or IV heart failure should not be routinely treated with β-blocking agents, but data regarding this patient population will soon be available from the BEST and COPERNICUS trials.

Once heart failure subjects reach a maintenance dose of a β-blocker, treatment should be maintained indefinitely because of the risk of deterioration on withdrawal. If it is necessary to treat a decompensated patient on maintenance β-blockade with a positive inotropic agent, a phosphodiesterase inhibitor rather than a β-agonist should be used because the hemodynamic effects of these inhibitors are not antagonized by β-blockade. \(^{115,116}\)

**Limitations of β-Blocker Therapy in Chronic Heart Failure**

Despite their proven efficacy in mild to moderate heart failure in patients with primary or secondary dilated cardiomyopathies, it is important to emphasize that β-blockers have limitations in their general application in heart failure populations. First and foremost is that many heart failure patients have contraindications to β-blockade, such as reactive airways disease, sinus node or conduction system disease with bradycardia, and advanced heart failure with hemodynamic decompensation. Another problem is that even in mild to moderate heart failure, initiation of therapy and titration of β-blocking agents can be difficult, requiring both persistence and knowledge of management maneuvers\(^ {70}\) that allow target doses to be achieved. A third problem is that for reasons that are not yet clear, some individuals do not respond to β-blockade in terms of favorable effects on myocardial function, and these individuals may have a worse outcome than patients treated with placebo. Some but not all of these problems might be overcome by the development of heart failure–designed “fourth-generation” β-blockers,\(^ {57}\) other effective types of antiadrenergic therapy, or β-blockers combined with positive inotropic agents.\(^ {117}\) The importance of the β-blocker data set is not that it demonstrates a “cure” for chronic heart failure but rather that it has shown that in some patients, prognosis can be substantially improved by medical therapy. This observation should provide the impetus to develop further types of treatment that improve the biological properties of the failing heart.

In summary, antiadrenergic therapy of chronic heart failure with β-blocking agents has evolved over a 25-year period from a contraindication to an established treatment for mild to moderate heart failure caused by primary or secondary dilated cardiomyopathies. Whether or not this therapy has value in other heart failure settings will be determined in ongoing and future studies.

**Acknowledgment**

I wish to thank Frank Stewart and Laurel Hunter for assistance in manuscript preparation and Doug Robertson for biostatistical support.

**References**


40. Quaile RA, Gilbert EM, Christian PE, Day FL, Mealey PC, Volkman K, Olsen SL, Bristow MR. Effects of carvedilol on systolic and diastolic...

KEY WORDS: drugs; heart failure; receptors, adrenergic, beta
β-Adrenergic Receptor Blockade in Chronic Heart Failure
Michael R. Bristow

Circulation. 2000;101:558-569
doi: 10.1161/01.CIR.101.5.558

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/101/5/558

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/