

Benefits of β -Blocker Therapy for Heart Failure

Weighing the Evidence

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Our understanding of factors contributing to the progression of heart failure has advanced dramatically over the past 2 decades. We have also gained considerable insight into the pharmacology of β -adrenergic receptor blockers (β -blockers). Based on this knowledge, we can now appreciate the potential of these drugs for the treatment of heart failure. Several β -blockers have been shown to be clinically effective in the treatment of heart failure. Critical evaluation of the evidence from basic research studies, as well as clinical trials in patients with heart failure, helps to delineate the theoretical and clinical benefits of β -blockers.

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Over the past several years, our understanding of the effect of activation of the renin-angiotensin system (RAS) and the sympathetic nervous system (SNS) on the pathophysiology of heart failure has resulted in the development of drugs that have improved morbidity and mortality associated with this chronic condition. Extensive basic research provided the scientific rationale for modulation of RAS activation in the treatment of heart failure, and clinical research has established the importance of angiotensin-converting enzyme (ACE) inhibitors in the treatment of patients with chronic heart failure. In addition, it has become clear that blockade of the SNS can have important clinical effects in patients with heart failure. We also have gained considerable knowledge of the interaction of the RAS and the SNS in the failing myocardium.

Activation of the SNS initially improves and maintains cardiac function. However, sustained sympathoadrenergic activation results in chronic elevation of norepinephrine levels and down-regulation of β_1 -receptors,^{1,2} which can be detrimental to cardiac function. Chronic elevation of plasma norepinephrine levels is also potentially cardiotoxic and is associated with poor prognosis in patients with heart failure.^{1,3}

The significant reductions in mortality and morbidity recently observed in large clinical trials of β_1 -selective (metoprolol succinate controlled release/extended release [CR/XL] and bisoprolol) and non-selective (carvedilol) agents indicate that pharmacologic blockade of β -adrenergic receptors results in considerable clinical improvement in patients with chronic heart failure. However, there are important differences in pharmacologic or ancillary properties (**Table 1**) among agents that may be clinically meaningful. The role of β -adrenergic receptor blockers (β -blockers) in the setting of the activated SNS that occurs in heart failure is the focus of this review.

BASIC RESEARCH EVIDENCE: ADRENERGIC MECHANISMS CONTRIBUTING TO HEART FAILURE

β -Adrenergic Receptor Signaling

The SNS is an important regulator of myocardial performance mediated principally by norepinephrine and its modulation of calcium entry into cardiomyocytes.⁴ Adrenergic neurohormones (eg, epinephrine and norepinephrine) affect activity or function of cardiomyocytes via neurohormonal binding at the β -receptor. Chronotropic and inotropic effects

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Table 1. Receptor Blockade and Ancillary Properties of β -Blockers Studied in Large Heart Failure Mortality Trials*

β -Blocker	Positive Mortality Trial	Receptor Blockade			Decreased Oxidative Stress	Decreased Apoptosis
		β_1	β_2	α_1		
Bisoprolol fumarate	Yes	Yes	No	No	NA	NA
Bucindolol hydrochloride	No	Yes	Yes	No	NA	NA
Carvedilol	Yes	Yes	Yes	Yes	Yes	Yes
Metoprolol tartrate IR	No	Yes	No	No	Yes	Yes
Metoprolol succinate CR/XL	Yes	Yes	No	No	NA	NA

*IR indicates immediate release; CR/XL, controlled release/extended release; and NA, not available.

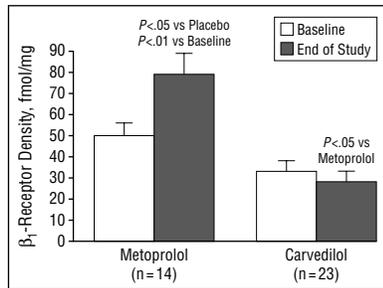


Figure 1. Comparison of the effect of metoprolol vs carvedilol on cardiac β_1 -receptor density. Data are mean \pm SEM. Adapted with permission from Gilbert et al.¹⁰

are regulated primarily by β_1 -adrenoreceptors that bind to norepinephrine with high affinity. In contrast, β_2 -adrenoreceptors bind with higher affinity to epinephrine.⁴

In the failing heart, enhanced, sustained sympathetic drive down-regulates β_1 -adrenoreceptors and desensitizes the β -adrenergic system.^{2,5} Alterations in the β -adrenergic system resulting from chronic heart failure include (1) down-regulation of β_1 -adrenergic receptors, (2) uncoupling of downstream pathways (stimulatory G proteins), and (3) up-regulation of β -adrenoreceptor kinase, leading to enhanced phosphorylation of β_1 - and β_2 -adrenoreceptors.⁶⁻⁹

Administration of β_1 -selective antagonists, such as metoprolol and bisoprolol, has been shown to (1) up-regulate cardiac β_1 -adrenergic receptors, thereby increasing cardiac responsiveness to exogenously administered catecholamines, and (2) recouple uncoupled β_2 -adrenoreceptors, thereby restoring normal signal transduction.⁶ In a comparison of metoprolol tartrate and carvedilol in 2 concurrent clinical trials, the β_1 -selective agent (metoprolol) increased β_1 -receptor density in en-

domyocardial membranes vs the nonselective β -blocker (carvedilol), which did not alter cardiac β -receptor number (**Figure 1**).¹⁰ These alterations, in addition to a possible change in receptor affinity, may explain the improvement in exercise capacity observed in some patients treated with β_1 -selective agents and not with a nonselective agent such as carvedilol.¹¹ Markers of myocardial function, such as left ventricular ejection fraction (LVEF), improved in both the metoprolol and carvedilol groups regardless of β -receptor activation.¹⁰ In a randomized, placebo-controlled study, metoprolol CR/XL significantly increased LVEF and left ventricular end-diastolic and end-systolic volumes relative to placebo after 24 weeks of therapy in patients with ischemic and dilated cardiomyopathy.^{12,13} This was also demonstrated in a subset of patients (n=41) with chronic heart failure enrolled in the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF); treatment with metoprolol CR/XL for 6 months resulted in significant increases in LVEF as well as significant decreases in left ventricular end-diastolic volume index and left ventricular end-systolic volume index compared with baseline.¹⁴

Calcium Handling

Contraction and relaxation of cardiac muscle are regulated by the concentration of intracellular free calcium (Ca^{2+}), which is controlled by release or uptake of Ca^{2+} by the sarcoplasmic reticulum.¹⁵ The role of β -blockade in modulating Ca^{2+} handling in the cardiomyocyte sarco-

plasmic reticulum has not been fully elucidated. However, it is clear that β -blockade-induced bradycardia results in prolonged diastolic filling and increased Ca^{2+} loading into the sarcoplasmic reticulum, causing augmentation of contraction during systole.^{5,16} Metoprolol also has been shown to reduce carnitine palmitoyl transferase I (CPT-I) activity in dogs with heart failure by redirecting substrate utilization, which may contribute to an increased rate of Ca^{2+} uptake in the sarcoplasmic reticulum and improvement in cardiac contractility.^{17,18} In addition to the positive impact of β -blockers on Ca^{2+} mobilization, these agents reduce myocardial oxygen consumption and may ameliorate the adverse effects of hypoxia.⁵

Cardiac Remodeling

A feature of myocardial dysfunction and progressive heart failure is cardiac remodeling with dilatation of the left ventricle. This process involves both cardiac hypertrophy and apoptosis or programmed cell death. The loss of cardiomyocytes and the development of fibrotic interstitial tissue result in compromised cardiac performance. Many factors have been identified that mediate hypertrophy, including adrenergic stimulation. In cultured cardiomyocytes, norepinephrine induces DNA and protein synthesis without compensatory cell division, leading to increased cardiomyocyte size. Both α_1 - and β -adrenoreceptors appear to be involved in this process.^{19,20}

Cardiomyocyte necrosis resulting from chronic catecholamine exposure has been well documented.¹ More recently, the importance of cell loss due to programmed cell death or apoptosis has been recognized.^{5,21-23} Cell death due to apoptosis occurs without an inflammatory reaction and as a result of intrinsic changes in intracellular gene-regulated proteins.²⁴ Cellular triggers that may lead to apoptosis are dominant features of the failing heart, including increased cytosolic calcium concentration, exposure of cardiac myocytes to hypoxia, and excess levels of norepinephrine.⁵ Incubation of cardiomyocytes in vitro with norepinephrine induces apoptosis,⁵ and

β_1 -adrenoreceptors appear to play a central role in this effect.²⁵⁻²⁷

It has been shown that the induction of cardiomyocyte apoptosis by incubation with norepinephrine can be attenuated with propranolol, a nonselective β -blocking agent.²⁵ In canine models of heart failure, treatment with metoprolol markedly reduces apoptosis in the myocardium and prevents progression of heart failure (Figure 2).^{23,28} The specific mechanisms of this anti-apoptotic effect are not fully understood, although there is evidence that metoprolol leads to enhanced expression of Bcl-2, a cellular oncoprotein that inhibits apoptosis.²⁸ Anti-apoptotic effects also have been demonstrated with carvedilol.²⁹ However, in vitro studies using cultured cells recently have shown that although β_1 antagonism inhibits apoptosis, β_2 antagonism increases apoptosis, thus suggesting a particular importance of β_1 selectivity.²⁵ However, the degree to which apoptosis plays a role in cardiac remodeling remains uncertain.

Oxidative Stress

Oxidative stress is thought to enhance the generation of oxygen-free radicals and may result in myocardiocyte damage and apoptosis. An association between heart failure and increased free radicals has been demonstrated in animal models and in patients with heart failure.^{30,31} The nonselective agent carvedilol has been shown to inhibit the formation of free radicals, block lipid peroxidation, and prevent oxygen radical-induced cell death in vitro; such effects have not been reported with metoprolol use. However, in a recent study comparing carvedilol with metoprolol treatment in heart failure patients, both agents reduced the level of oxidative stress to the same degree, which is most likely related to the improvement in heart failure status, indicating no additional antioxidant benefit with carvedilol (Figure 3).³²

EVIDENCE FROM CLINICAL TRIALS

Recent randomized, placebo-controlled clinical trials have evaluated the survival benefit of β -block-

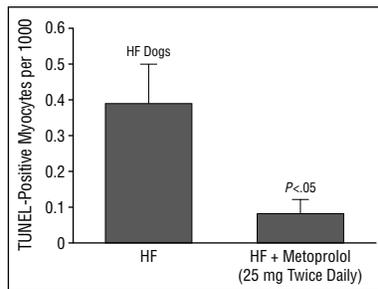


Figure 2. Apoptosis in heart failure (HF). TUNEL indicates TdT-mediated dUTP nick-end labeling.²⁸

ers added to standard therapy with ACE inhibitors and diuretics for the treatment of heart failure. We now know that β -blockade has beneficial effects on both morbidity and mortality in patients with heart failure. In fact, the mortality benefit of β -blockade in addition to standard therapies exceeds that of any other current pharmacologic intervention in similar patient populations, including available clinical trial data with ACE inhibitor therapy. These drugs provide an added effect beyond that achieved with ACE inhibitors.

Randomized Clinical Trials: New York Heart Association Class II to IV

Four large trials have been completed in the last 5 years and, in general, they support the concept that β -adrenergic blockade is beneficial in heart failure. The initial US Carvedilol Heart Failure Trials Program, which was not designed to assess mortality, was followed by the Cardiac Insufficiency Bisoprolol Study-II (CIBIS-II), a trial powered to study the mortality benefit of bisoprolol use in patients with heart failure.³³ The largest β -blocker trial, MERIT-HF,^{34,35} was reported shortly after the first 2 trials and was followed by the Beta-Blocker Evaluation of Survival Trial (BEST).³⁶ The most recent mortality trial, the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial, was the last of the randomized mortality trials completed, and it focused on patients with severe heart failure.³⁷ All 4 mortality trials, CIBIS-II, MERIT-HF, BEST, and COPERNICUS, provided additional insight into the mortality benefits of β -blocker use in patients with heart failure.

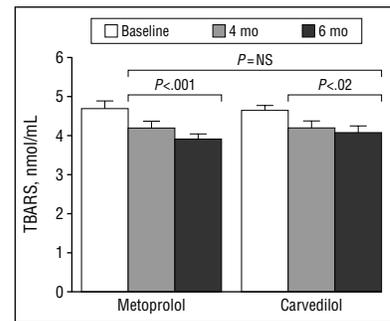


Figure 3. Mean \pm SEM thiobarbituric acid-reactive substance (TBARS) values for patients who completed the protocol at baseline, month 4, and month 6 for metoprolol and carvedilol, respectively. Differences between baseline and month 6 were significant for both metoprolol ($P < .001$) and carvedilol ($P = .02$) as indicated by within-group paired t tests. The overall analysis of variance performed between groups for all time points was not significant (NS). Adapted with permission from Kukin et al.³²

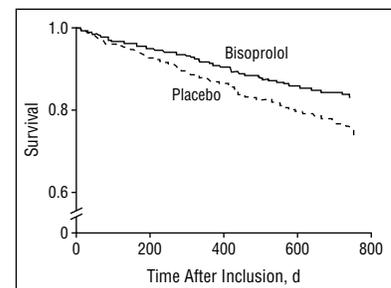


Figure 4. Survival curve from the Cardiac Insufficiency Bisoprolol Study-II (CIBIS-II) trial ($P < .001$). Reprinted with permission from CIBIS-II Investigators.³³

Both CIBIS-II and MERIT-HF examined the effect of β_1 -selective blockade using bisoprolol and metoprolol CR/XL, respectively. The CIBIS-II trial³³ included 2647 symptomatic patients, limited to those with New York Heart Association (NYHA) class III or IV heart failure with LVEF of 35% or less. Bisoprolol is a long-acting, once-daily β_1 -blocker. Patients with class IV disease accounted for 17% of the population. In CIBIS-II, 384 deaths were reported, 156 (11.8%) in the bisoprolol group and 228 (17.3%) in the placebo group,³³ representing a 34% risk reduction for all-cause mortality and a 26% risk reduction for death due to worsening heart failure (Figure 4). In MERIT-HF, the use of metoprolol CR/XL (a controlled-release/extended-release formulation of metoprolol succinate that also provides consistent 24-hour β_1 blockade) was investigated. At the peak target dose of 200 mg once daily, β_1 -receptor blockade is almost

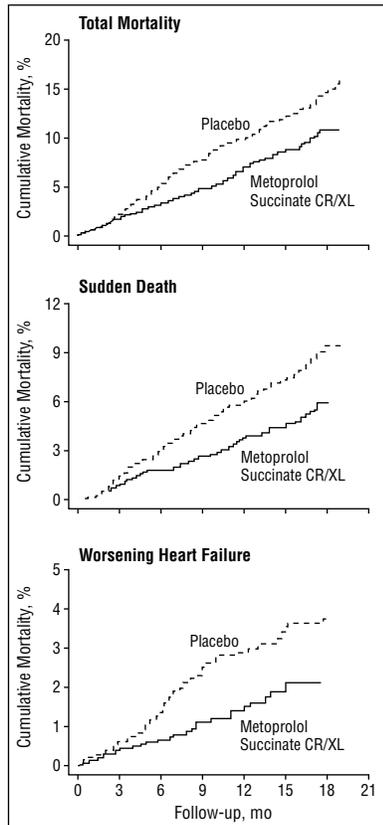


Figure 5. Kaplan-Meier curve of cumulative percentage of total mortality ($P = .006$, adjusted for interim analyses; $P < .001$, nominal), sudden death ($P < .001$), and worsening heart failure ($P = .002$) in the Metoprolol Controlled Release/Extended Release (CR/XL) Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). Reprinted with permission from MERIT-HF Study Group.³⁴

complete and corresponds to 40% to 80% of maximum effect based on exercise heart rate.³⁸ The MERIT-HF trial³⁴ included 3991 ambulatory patients with NYHA class II, III, or IV heart failure with LVEF of 40% or less, who were stabilized on standard heart failure therapy, including ACE inhibitors and diuretics. Most patients (96.4%) had NYHA class II or III heart failure; 145 patients (3.6%) had class IV failure. In addition, half of the patients were older than 65 years, and one third had LVEF less than 25%. Overall, a 34% risk reduction for all-cause mortality was reported in MERIT-HF, with a 49% risk reduction for death due to worsening heart failure and a 41% decrease in sudden death (**Figure 5**).³⁵ Sudden death was the most common cause of mortality, accounting for more than 60% of all deaths.³⁴ In addition to its mortality benefit, metoprolol CR/XL use decreased the combined event rate of all-

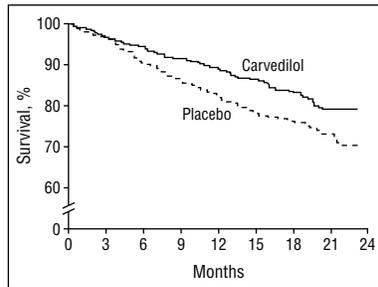


Figure 6. Kaplan-Meier analysis of survival from the Carvedilol Prospective Randomized Cumulative Survival trial ($P < .001$, adjusted). Reprinted with permission from Packer et al.³⁷

cause mortality and heart failure hospitalizations by 31%.³⁴ Results of subgroup analyses based on a variety of patient characteristics including age, sex, race, and etiology of heart disease are consistent with results observed in the primary study group.

Two nonselective β -blockers, carvedilol and bucindolol, have also been evaluated in clinical trials of heart failure. The US Carvedilol Heart Failure Trials Program included 1094 patients and evaluated a nonselective β -blocker for the treatment of heart failure due to systolic dysfunction. The US Carvedilol Heart Failure Trials Program was designed as 4 separate protocols and was not designed to assess mortality; however, safety analyses unexpectedly demonstrated a mortality benefit.^{4,39} Consequently, the program was terminated prematurely with a limited number of mortality events (31 placebo-treated patients [7.8%] died compared with 22 carvedilol-treated patients [3.2%]).³⁹

The observations from the recently reported BEST are more difficult to interpret. Patients with more advanced heart failure and ejection fractions of 35% or less were included in BEST. Although a beneficial trend was observed with bucindolol use, a nonselective β -blocker, the results did not reach statistical significance and failed to demonstrate a significant survival benefit.³⁶ There were 411 deaths (14.9%) in the bucindolol group and 449 deaths (16.6%) in the placebo group during approximately 2 years of follow-up. It is not clear why no significant survival effect was observed with bucindolol use. However, possible explanations may include differences in the study population, the specific phar-

macologic properties of bucindolol, or both.

The question regarding comparative efficacy of immediate-release metoprolol and carvedilol is currently under investigation in the Carvedilol or Metoprolol European Trial (COMET). This study is comparing metoprolol tartrate (rather than metoprolol succinate CR/XL) with carvedilol in approximately 3000 patients with heart failure in Europe.⁴ Because this trial is not a direct comparison of carvedilol with metoprolol CR/XL, the agent used in MERIT-HF, the usefulness of the results will be somewhat limited.

Results in Patients With Severe Heart Failure

The COPERNICUS trial was designed specifically to examine the mortality effect of carvedilol in patients with severe heart failure with LVEF less than 25%.³⁷ The study enrolled 2289 patients with severe heart failure characterized as having symptoms at rest or with minimal exertion and demonstrated a 35% decrease in mortality (95% confidence interval, 19%-48%; $P < .001$) (**Figure 6**). The placebo population had an annual mortality rate of 18.5% and a mean LVEF of 20%. The results were consistent across all predetermined prespecified characteristics, and treatment was well tolerated.

Subgroup analysis of similar patients included in MERIT-HF with NYHA class III or IV and LVEF less than 25% ($n = 795$) confirmed these findings.⁴⁰ In the MERIT-HF severe heart failure subgroup, not only did metoprolol CR/XL use result in a 39% risk reduction for total mortality, it also resulted in a 55% risk reduction for death due to worsening heart failure and a 45% risk reduction for sudden death (**Figure 7**).⁴⁰ In addition, metoprolol CR/XL use decreased the combined end point of all-cause mortality plus all-cause hospitalization by 29%. The drug was well tolerated, with 31% fewer all-cause withdrawals and 45% fewer withdrawals due to worsening heart failure in the metoprolol CR/XL group compared with the placebo population (**Figure 8**). In this severe heart failure subgroup of MERIT-HF, metoprolol CR/XL therapy also

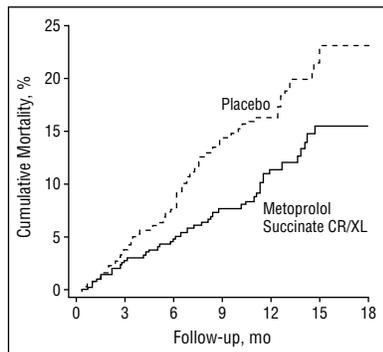


Figure 7. Mortality curve from post hoc subgroup analysis of patients with severe heart failure in the Metoprolol Controlled Release/Extended Release (CR/XL) Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). Adapted with permission from Goldstein et al.⁴⁰

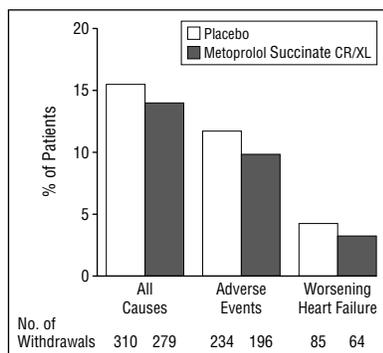


Figure 8. Reasons for withdrawal of study medication in the Metoprolol Controlled Release/Extended Release (CR/XL) Randomized Intervention Trial in Congestive Heart Failure.³⁴

resulted in an improvement in NYHA functional class ($P=.003$) compared with placebo.⁴⁰ Subgroup analysis of NYHA class III and IV patients with LVEF less than 25% in MERIT-HF and COPERNICUS data is given in **Table 2**. It can be seen that both studies are similar in regard to their LVEF and annual placebo mortality rate.

Dosing and Tolerability

The trials discussed in the present review generally included ambulatory patients who were stable on the accepted contemporary therapy for heart failure (ACE inhibitors, digitalis, and diuretics).^{33,34,36,39} Patients with heart rates below 60 to 68 beats per minute and systolic blood pressures below 90 to 100 mm Hg were excluded from the studies. With the exception of the US Carvedilol Heart Failure Trials Program, which had an active run-in period,

Table 2. Subgroup Analysis for NYHA Class III-IV Patients With LVEF Less Than 25% in COPERNICUS and MERIT-HF Trials

	COPERNICUS ³⁷ (n = 2289)	MERIT-HF ⁴⁰ (Severe HF Subgroup) (n = 795)
Mean LVEF, %	20	19
Mortality, %		
Placebo	18.5	19.1
β -blocker	11.4	11.7
Risk reduction, % (95% CI)	35 (0.52-0.81)	39 (0.11-0.58)
P value	<.001	<.009

*NYHA indicates New York Heart Association; LVEF, left ventricular ejection fraction; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival; MERIT-HF, Metoprolol Controlled Release/Extended Release Randomized Intervention Trial in Congestive Heart Failure; and CI, confidence interval.

Table 3. Recommended Doses of β -Blockers for Patients With Chronic Heart Failure

β -Blocker	Dosing Schedule	Initial Dose, mg	Maximum Daily Dose, mg
Bisoprolol fumarate	Once daily	1.25	10
Carvedilol	Twice daily	3.125	50/100*
Metoprolol Succinate Controlled Release/Extended Release	Once daily	12.5/25†	200

*Dose of 25 mg twice daily for patients with a body weight under 85 kg and 50 mg twice daily for patients with a body weight of 85 kg or over.

†Dose of 25 mg recommended for New York Heart Association (NYHA) class II patients and 12.5 mg for NYHA class III-IV patients.

the trials were initiated after a period of stabilization on standard therapy followed by a placebo run-in period. Patients completing the run-in periods were randomized in their respective trials and were gradually up-titrated over a 6- to 8-week period to a total maximum target dose (10 mg of bisoprolol daily, 50 mg [<75 kg] or 100 mg [>75 kg] of bucindolol hydrochloride twice daily, or 200 mg of metoprolol CR/XL daily; maximum target doses of carvedilol varied among the 4 protocols, ranging from 6.25 mg twice daily to 50 mg twice daily).^{33,34,36,39} These drugs were well tolerated; most patients were titrated to maximum or near maximum doses. For example, at completion of MERIT-HF, 64% of patients had achieved the maximum target dose of 200 mg of metoprolol CR/XL per day, 87% had achieved a dose of 100 mg or more of metoprolol CR/XL per day,⁴¹ and 43% of patients in CIBIS-II had achieved the target dose of 10 mg of bisoprolol per day.⁴² The dosing schedules used in these 3 trials are given in **Table 3**. There were no differences in discontinuations between the active and placebo arms of these trials, although assessment of

both adverse events and discontinuations in the US Carvedilol Heart Failure Trials Program is confounded because of the open-label run-in phase. Because of this, patients who died during the run-in phase or did not tolerate carvedilol were excluded. In MERIT-HF, compared with the placebo group, withdrawal of the study drug from all causes was 10% lower (Figure 8) and withdrawal due to worsening heart failure was 25% lower in the metoprolol CR/XL group, although this finding did not reach statistical significance.³⁵ Contrary to common belief, these trials demonstrate that β -blockers are well tolerated in patients with heart failure; with initiation at low doses and careful titration, most patients can achieve a maximum therapeutic dose. In the setting of worsening heart failure during β -blocker therapy, the β -blocker dose should not be up-titrated further and, if necessary, can be decreased gradually.

Both carvedilol and metoprolol are highly lipophilic compounds and are metabolized and cleared by the liver. In the setting of hepatic congestion, dosage reduction may be required. Bisoprolol is less lipophilic and exhibits both hepatic

and renal clearance. There does not appear to be any significant interaction with other cardiac drugs, including warfarin and digoxin.²

COMMENT

It is clear that circulating neurohormones can alter cell contractile function and that almost all β -blocking agents have the ability to improve cell function, resulting in increased ejection fraction, improved diastolic relaxation and myocardial energetics, and decreased end-diastolic pressures. The mechanism by which β -blockers alter the electrophysiologic properties of the ventricle to decrease the occurrence of sudden death is, however, still uncertain. In the pilot study for MERIT-HF, metoprolol CR/XL decreased ventricular ectopy and the frequency of non-sustained ventricular tachycardia associated with an increase in LVEF.¹³ These results provide some mechanistic support for the benefit of β -blocker use in suppressing sudden death as observed in the clinical trials MERIT-HF and CIBIS-II.

Basic research evidence regarding the effects of β -blockers on apoptosis and oxidative stress also suggests little difference between agents. Evidence that catecholamines, particularly norepinephrine, can cause apoptosis in isolated myocytes supports the potential lethality of these neurohormones to these cells. Both β_1 -selective and nonselective β -blockers have been shown to reduce apoptosis in animal models of heart failure; however, there is no evidence linking a reduction in apoptosis with improved clinical outcomes in patients with heart failure.^{23,28,29} Similarly, treatments with carvedilol and metoprolol have been shown to reduce oxidative stress in patients with heart failure; however, this is more likely a result of improved heart failure status rather than a direct effect of either agent.

The evidence that catecholamines, particularly norepinephrine, cause β_1 -adrenergic down-regulation and that β -adrenergic antagonists counteract this effect set the stage for the evaluation of β -blocker use in patients with heart failure. Demonstrated increases in β_1 -adrenoreceptor density follow-

ing metoprolol treatment appear to correlate with enhanced exercise capacity. However, improvement in ejection fraction appears to be independent of receptor up-regulation because a positive effect has been observed with the cardioselective agent metoprolol, which up-regulates receptors, and the nonselective agent carvedilol, both of which appear to have no effect on receptor density.¹⁰

The findings of the recent clinical trials have added immensely to our understanding of the benefits of β -blocker use in patients with heart failure. There is now abundant evidence to indicate that β -blockers have a significant effect on the failing ventricle and that these benefits are translated into improved survival and decreased hospitalization of patients with heart failure. It is also clear from these studies that they have an incremental effect on mortality when added to ACE inhibitor therapy.

The question of whether conclusions drawn from randomized clinical trials can be generalized to patients in the overall population is frequently, and quite appropriately, raised. It is imperative that clinical trials include patients who are representative of the general population. The patients included in these trials are symptomatic, and many of them have severe exercise limitation. However, both ends of the clinical spectrum have not been included in these trials.

None of the studies described above recruited patients with NYHA class I heart failure. However, some extrapolations can be made from the Australia/New Zealand carvedilol trial.⁴³ In that study, investigators recruited asymptomatic, post-myocardial infarction patients with decreased ejection fractions and observed a significant benefit on combined mortality and hospitalization. Further, there is additional evidence that use of β -blockers improves survival after myocardial infarction from the Beta-Blocker Heart Attack Trial (BHAT) in patients with heart failure⁴⁴ and from the recent Carvedilol Post-Infarction in Survival Control in Left-Ventricular Dysfunction (CAPRICORN) trial in patients with decreased ejection fraction.⁴⁵

The MERIT-HF, CIBIS-II, and COPERNICUS trials indicate that

β -blockers are not only safe for the treatment of severe heart failure, they are also extremely effective in decreasing mortality and the need for hospitalization. It must be emphasized, however, that although some patients enrolled in these trials were classified as experiencing severe heart failure, they were generally stable on therapy with ACE inhibitors and diuretics without severe fluid overload. In addition, most patients were ambulatory with stable blood pressure. Whether β -blocker therapy has a role in patients with more compromised heart failure with fluid overload and hypotension remains to be studied. At the present, a series of studies are under way to evaluate the role of temporary intravenous support with inotropic agents as a bridge to β -blocker therapy in patients with more advanced heart failure who are hemodynamically unstable.⁴⁶ These studies are important in demonstrating the safety of β -blocker use in this defined population with severe heart failure. It is important that the patient population assessed in these studies be understood because β -blocker therapy has not been shown as yet to provide acute improvement and should not be viewed as lifesaving therapy in a patient whose condition is progressively deteriorating. Improvements in LVEF take place over a number of weeks.⁴⁷

More important, however, β -blocker therapy has a greater public health benefit potential in the larger population of patients with mild to moderate heart failure. Although these patients have a lower mortality rate, they represent most patients with heart failure. The relative benefit of β -blocker use in mild to moderate heart failure is similar to that in patients at higher risk, but the absolute benefit is much greater in the high-risk patients.

The true test of the efficacy and benefit of a specific β -blocker treatment remains the appropriately designed clinical trial. The BEST study results indicate that it cannot be assumed that the benefit of β -blocker use in patients with heart failure is a class effect. Persuasive clinical trial evidence in large numbers of patients with class II to IV stable heart failure demonstrates that mortality

and morbidity are improved with use of the β_1 -selective agents metoprolol CR/XL and bisoprolol and with the nonselective agent carvedilol. Moreover, the clinical outcome results of these trials are remarkably similar. Blockade of the β_1 -receptor appears to be the common denominator, and therefore a critical element responsible for the morbidity and mortality benefits observed with the use of these agents. Whether β_2 - and α_1 -receptor blockade provides additional benefit is not clear.¹¹ There appears to be little difference in regard to the efficacy of selective vs nonselective β -blockers in randomized clinical trials; however, there does appear to be some difference in their hemodynamic effects.¹¹

Are there other properties that might influence the effectiveness of one β -blocker vs another? Carvedilol and bucindolol have been described as third-generation β -blockers because they acutely elicit vasodilatation. For carvedilol, this reduction in afterload is a result of α_1 -receptor blockade and offsets, to some degree, the early negative inotropic effect of β -blockade, potentially improving tolerability. However, this vasodilator effect can result in orthostasis during initiation and titration; thus patients must be monitored closely during this time. Over the long term, studies have demonstrated that tolerance develops, and the hemodynamic effects of α_1 -blockade with carvedilol are no longer apparent. Convenient once-daily dosing also is important in patients with heart failure. Both bisoprolol and metoprolol CR/XL are administered once daily and may improve compliance in some patients; however, of these 2 agents, only metoprolol CR/XL (and carvedilol, which requires twice-daily dosing) are approved for the treatment of heart failure in the United States.

CONCLUSIONS

The primary criterion for selection of a β -blocker treatment should be proven effectiveness in reducing mortality and morbidity in patients with heart failure in a large prospective randomized trial. We now have abundant information to indicate that 3 β -blockers—metoprolol CR/XL, bi-

soprolol, and carvedilol—have been proven to be effective in this regard. Secondary criteria are those that encourage compliance, including tolerability (particularly during the titration phase), dosing frequency (daily vs twice daily), and medication cost. These factors should be considered when β -blockers are prescribed for heart failure. Currently, with fewer than 20% of eligible patients with heart failure receiving a β -blocker treatment, the goal of practicing physicians should be to ensure that a β -blocker is considered as part of the standard treatment regimen for all patients with mild to moderate heart failure.

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REFERENCES

- Mann DL, Kent RL, Parsons B, Cooper G IV. Adrenergic effects on the biology of the adult mammalian cardiocyte. *Circulation*. 1992;85:790-804.
- Bristow MR. β -Adrenergic receptor blockade in chronic heart failure. *Circulation*. 2000;101:558-569.
- Cohn JN, Levine TB, Olivari MT, et al. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. *N Engl J Med*. 1984;311:819-823.
- Carson PE. Beta blocker treatment in heart failure. *Prog Cardiovasc Dis*. 1999;41:301-322.
- Sabbah HN. The cellular and physiologic effects of beta blockers in heart failure. *Clin Cardiol*. 1999; 22(suppl V):V16-V20.
- Bristow MR. Mechanism of action of beta-blocking agents in heart failure. *Am J Cardiol*. 1997; 80:26L-40L.
- Bristow MR, Ginsburg R, Umans V, et al. β_1 - and β_2 -adrenergic-receptor subpopulations in non-failing and failing human ventricular myocardium: coupling of both receptor subtypes to muscle contraction and selective β_1 -receptor down-regulation in heart failure. *Circ Res*. 1986; 59:297-309.
- Brodde OE, Schüler S, Kretsch R, et al. Regional distribution of β -adrenoceptors in the human heart: coexistence of functional β_1 - and β_2 -adrenoceptors in both atria and ventricles in severe congestive cardiomyopathy. *J Cardiovasc Pharmacol*. 1986;8:1235-1242.
- Koch WJ, Inglese J, Stone WC, Lefkowitz RJ. The binding site for the β_7 subunits of heterotrimeric G proteins on the β -adrenergic receptor kinase. *J Biol Chem*. 1993;268:8256-8260.
- Gilbert EM, Abraham WT, Olsen S, et al. Comparative hemodynamic, left ventricular functional, and antiadrenergic effects of chronic treatment with metoprolol versus carvedilol in the failing heart. *Circulation*. 1996;94:2817-2825.
- Metra M, Giubbini R, Nodari S, Boldi E, Modena MG, Dei Cas L. Differential effects of beta-blockers in patients with heart failure: a prospective, randomized, double-blind comparison of the long-term effects of metoprolol versus carvedilol. *Circulation*. 2000;102:546-551.
- The RESOLVD Investigators. Effects of metoprolol CR in patients with ischemic and dilated cardiomyopathy: the randomized evaluation of strategies for left ventricular dysfunction pilot study. *Circulation*. 2000;101:378-384.
- Goldstein S, Kennedy HL, Hall C, et al. Metoprolol CR/XL in patients with heart failure: a pilot study examining the tolerability, safety, and effect on left ventricular ejection fraction. *Am Heart J*. 1999; 138:1158-1165.
- Groenning BA, Nilsson JC, Sondergaard L, Fritzhansen T, Larsson HBW, Hildebrandt PR. Anti-remodeling effects on the left ventricle during beta-blockade with metoprolol in the treatment of chronic heart failure. *J Am Coll Cardiol*. 2000;36: 2072-2080.
- Arai M, Matsui H, Periasamy M. Sarcoplasmic reticulum gene expression in cardiac hypertrophy and heart failure. *Circ Res*. 1994;74:555-564.
- Hasenfuss G, Reinecke H, Studer R, et al. Relation between myocardial function and expression of sarcoplasmic reticulum Ca^{2+} -ATPase in failing and nonfailing human myocardium. *Circ Res*. 1994;75:434-442.
- Panchal AR, Stanley WC, Kerner J, Sabbah HN. Beta-receptor blockade decreases carnitine palmitoyl transferase I activity in dogs with heart failure. *J Card Fail*. 1998;4:121-126.
- Rupp H, Schulze W, Vetter R. Dietary medium-chain triglycerides can prevent changes in myosin and SR due to CPT-1 inhibition by etomoxir. *Am J Physiol*. 1995;269:R630-R640.
- Clark WA, Rudnick SJ, LaPres JJ, Andersen LC, LaPointe MC. Regulation of hypertrophy and atrophy in cultured adult heart cells. *Circ Res*. 1993; 73:1163-1176.
- Colucci WS. The effects of norepinephrine on myocardial biology: implications for the therapy of heart failure. *Clin Cardiol*. 1998;21(suppl 1):120-124.
- Narula J, Haider N, Virmani R, et al. Apoptosis in myocytes in end-stage heart failure. *N Engl J Med*. 1996;335:1182-1189.
- Sabbah HN, Sharov VG, Goldstein S. Programmed cell death in the progression of heart failure. *Ann Med*. 1998;30(suppl 1):33-38.
- Sharov VG, Sabbah HN, Shimoyama H, Goussev AV, Lesch M, Goldstein S. Evidence of cardiocyte apoptosis in myocardium of dogs with chronic heart failure. *Am J Pathol*. 1996;148: 141-149.
- Sabbah HN. Apoptotic cell death in heart failure. *Cardiovasc Res*. 2000;45:704-712.
- Communal C, Singh K, Sawyer DB, Colucci WS. Opposing effects of β_1 - and β_2 -adrenergic receptors on cardiac myocyte apoptosis: role of a toxin-sensitive G protein. *Circulation*. 1999;100:2210-2212.
- Iwai-Kanai E, Hasegawa K, Araki M, Kakita T, Morimoto T, Sasayama S. Alpha- and beta-adrenergic pathways differentially regulate cell type-specific apoptosis in rat cardiac myocytes. *Circulation*. 1999;100:305-311.
- Singh K, Communal C, Sawyer DB, Colucci WS.

- Adrenergic regulation of myocardial apoptosis. *Cardiovasc Res.* 2000;45:713-719.
28. Sabbah HN, Sharov VG, Gupta RC, Todor A, Singh V, Goldstein S. Chronic therapy with metoprolol attenuates cardiomyocyte apoptosis in dogs with heart failure. *J Am Coll Cardiol.* 2000;36:1698-1705.
 29. Ruffolo RR Jr, Feuerstein GZ. Carvedilol: preclinical profile and mechanisms of action in preventing the progression of congestive heart failure. *Eur Heart J.* 1998;19(suppl B):B19-B24.
 30. Dhalla AK, Hill MF, Singal PK. Role of oxidative stress in transition of hypertrophy to heart failure. *J Am Coll Cardiol.* 1996;28:506-514.
 31. McMurray J, Chopra M, Smith WE, Dargie HJ. Free radical activity in chronic heart failure: evidence for trans-myocardial oxidative stress [abstract 2247]. *Circulation.* 1990;82(suppl III):III-566.
 32. Kukin ML, Kalman J, Charney RH, et al. Prospective, randomized comparison of effect of long-term treatment with metoprolol or carvedilol on symptoms, exercise, ejection fraction, and oxidative stress in heart failure. *Circulation.* 1999;99:2645-2651.
 33. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet.* 1999;353:9-13.
 34. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet.* 1999;353:2001-2007.
 35. Hjalmarson Å, Goldstein S, Fagerberg B, et al. Effect of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). *JAMA.* 2000;283:1295-1302.
 36. Beta-Blocker Evaluation of Survival Trial Investigators. A trial of the β -blocker bucindolol in patients with advanced chronic heart failure. *N Engl J Med.* 2001;344:1659-1667.
 37. Packer M, Coats AJS, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med.* 2001;344:1651-1658.
 38. Abrahamsson B, L cker P, Olofsson B, et al. The relationship between metoprolol plasma concentration and beta 1-blockade in healthy subjects: a study on conventional metoprolol and metoprolol CR/ZOK formulations. *J Clin Pharmacol.* 1990;30:S46-S54.
 39. Packer M, Bristow MR, Cohn JN, et al, for the US Carvedilol Heart Failure Study Group. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *N Engl J Med.* 1996;334:1349-1355.
 40. Goldstein S, Fagerberg B, Hjalmarson A, et al, for the MERIT-HF Study Group. Metoprolol controlled release/extended release in patients with severe heart failure: analysis of the experience in the MERIT-HF study. *J Am Coll Cardiol.* 2001;38:932-938.
 41. Goldstein S, Hjalmarson Å. The mortality effect of metoprolol CR/XL in patients with heart failure: results of the MERIT-HF trial. *Clin Cardiol.* 1999;22(suppl 5):V30-V35.
 42. McMurray JJV. Major β -blocker mortality trials in chronic heart failure: a critical review. *Heart.* 1999;82(suppl IV):IV14-IV22.
 43. Australia/New Zealand Group Heart Failure Research Collaborative Group. Randomised, placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischaemic heart disease. *Lancet.* 1997;349:375-380.
 44. Chadda K, Goldstein S, Byington R, Curb JD. Effect of propranolol after acute myocardial infarction in patients with congestive heart failure. *Circulation.* 1986;73:503-510.
 45. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet.* 2001;357:1385-1390.
 46. Shakar SF, Abraham WT, Gilbert EM, et al. Combined oral positive inotropic and beta-blocker therapy for treatment of refractory class IV heart failure. *J Am Coll Cardiol.* 1998;31:1336-1340.
 47. Hall SA, Cigarroa CG, Marcoux L, Risser RC, Grayburn PA, Eichhorn EJ. Time course of improvements in left ventricular function, mass and geometry in patients with congestive heart failure treated with beta-adrenergic blockade. *J Am Coll Cardiol.* 1995;25:1154-1161.