Beta-Adrenergic Blocking Drugs in Severe Heart Failure

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Beta-adrenergic blocking drugs have been shown to improve survival and well-being of patients with mild to moderate heart failure. In more advanced heart failure, the relationship between the short-term hemodynamic support afforded by activation of the sympathetic nervous system and the harm that results from excess sympathetic activation is more complex. Not all studies of ß-adrenergic blocking drugs or antiadrenergic therapy have shown benefit. The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial has revealed that the combined nonselective ß-adrenergic and α-adrenergic receptor blocking drug carvedilol produces an important salutary effect on the natural history of advanced heart failure. Mortality was reduced by 35% in the carvedilol group, from an annual (Kaplan-Meier) rate of 18.5% to 11.4%. All-cause hospitalizations were reduced by 20% and hospitalization from heart failure by 33%. Even amongst the subgroups at highest risk, no subpopulation could be identified that did not appear to benefit. The trial supports extending the population of those with chronic heart failure who should be routinely treated with ß-adrenergic blocking drugs (in addition to angiotensin-converting enzyme inhibition therapy) to patients with more advanced disease.

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In health, the sympathetic nervous system appears to function to prepare the entire body for short bursts of physical activity such as may be required for fight or flight. This purpose, appreciated and described by Cannon,[1] recognized that the sympathetic nervous system is usually not active above a basal level and in fact is counter-regulated to some extent by some of the opposing influences of the parasympathetic nervous system, which is usually dominant at rest and for much of any 24-hour period. In some disease states—and especially

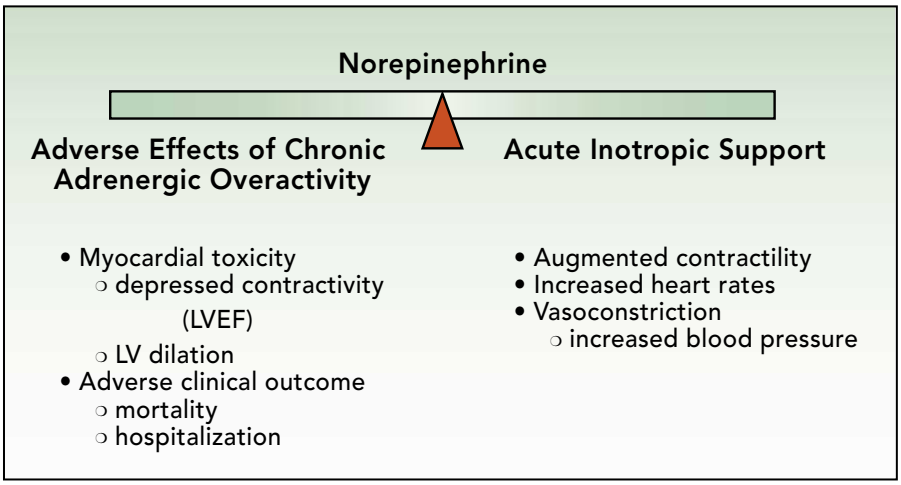

Figure 1. *Benefit versus harm of sympathetic activation. LV, left ventricle; LVEF, left ventricular ejection fraction.*

in heart failure—the autoregulation that normally acts to augment sympathetic activity becomes deranged, resulting in chronic and persistent activation of the sympathetic nervous system.[2] Despite attempts at "downstream" desensitization mechanisms, such as uncoupling, internalization, and decreased density of myocardial β_1-adrenergic receptors, the heart of an individual with heart failure is exposed to high sustained levels of sympathetic activity.[3–6] The relationship between potential benefit and harm from excess adrenergic activity is shown in Figure 1.

Although contractile support and an increase in heart rate (the inotropic and chronotropic actions of norepinephrine) may initially serve to maintain cardiac output, over time the inotropic support is diminished by loss of β_1-adrenergic receptors, and the harmful actions predominate.[3] There are clearly both short-term (increased myocardial oxygen demand, proarrhythmia) and long-term (depressional myocardial contractility, abnormal left ventricular remodeling, abnormal gene expression) adverse effects of chronic excess sympathetic activation. Moreover, in the periphery sympathetic activation contributes to increases in impedance and exacerbates salt and water retention through vasoconstrictor actions on the circulation and direct effects on the kidney.

ance of the failing heart. In mild heart failure, the degree of hemodynamic compromise in patients already receiving diuretics and drugs that modulate the renin–angiotensin–aldosterone system is mild. Plentiful evidence supports the concept that any mild, barely detectable, initial fall in contractility is rapidly reversed by the long-term improvement in contractility and sustained improvement in hemodynamics that are part of the chronic response to β-adrenergic blocking drugs used to treat heart failure.[6,7] This is especially true if the drugs are introduced at low doses and gradually uptitrated and if drugs with vasoconstrictor properties (such as the nonselective, nonvasodilating agent propranolol) are avoided.

In more severe heart failure, the balance between an initial fall in myocardial contractility and the long-term benefits mediated through

The heart of an individual with heart failure is exposed to high sustained levels of sympathetic activity.

Against this constellation of adverse effects of sympathetic activation in an individual with heart failure has to be balanced the degree of support provided to the contractile performtempering of excess chronic sympathetic activity may be more precarious. Indeed, some earlier studies prior to the Carvedilol Prospective Randomized Cumulative Survival

Table 1
Placebo Mortality Rate and the Reduction in Mortality from Beta-Adrenergic Blocking Drugs Prior to the COPERNICUS Trial

	Placebo Mortality Rate	Reduced Mortality Benefits	Proportion of Patients with Class IV Heart Failure
U.S. Carvedilol Program[16]	11.1%	65%	3%
MERIT-HF[10]	11.0%	34%	4%
CIBIS-II[9]	13.2%	34%	16%
BEST[12]	17.0%	10%	8%

(COPERNICUS) trial suggested a possible diminution of benefit as the disease severity, assessed from the prognoses of the group under evaluation, became more advanced (Table 1). Some of the subtleties of the interplay between harm from excess chronic sympathetic activity and support for the failing myocardium in advanced heart failure can be appreciated from an examination of the MOXCON trial.[8]

The MOXCON Trial

The Moxonidine Congestive Heart Failure (MOXCON) trial was an evaluation of an approach to protecting patients with heart failure from excess sympathetic activity by using a drug that acts principally on the brain to reduce the "central" release of norepinephrine.[8] The drug, moxonidine, worked to reduce norepinephrine levels, but instead of the hoped-for decrease in mortality and improved outcomes, the opposite effect was seen. More people randomized to moxonidine died. The findings of the MOXCON trial showed that norepinephrine does indeed play a role in supporting the failing heart and that a substantial and presumably sustained reduction in norepinephrine is detrimental.[8] In contrast, successful antiadrenergic therapy in heart failure has been confined to drugs that act as competitive inhibitors of β-adrenergic receptors. In fact, only three β-adrenergic blocking drugs have been shown to improve survival in randomized trials,[6,9,10] and it is well established that β-adrenergic blocking drugs, perhaps more than most other classes of therapeutic agents, differ in their pharmacology and antiadrenergic potential (Table 2).

Table 2
Antiadrenergic Actions of Beta-Adrenergic Blocking Drugs

	ß$_1$ Receptor	ß$_2$ Receptor	α$_1$ Receptor	No Upregulation of ß$_1$ Receptor	Reduction in Myocardial Norepinephrine	No ISA
Metoprolol	+					+
Bisoprolol	+					+
Carvedilol	+	+	+	+	+	+
Bucindolol	+	+	_	+	++	?

ISA, intrinsic sympathomimetic activity.

The BEST Trial

Bucindolol is a nonselective β-adrenergic blocking drug that had been shown in pilot trials to cause a dose-dependent improvement in left ventricular ejection fraction (LVEF) in patients with heart failure[11] but which also, and perhaps significantly, showed a trend toward less improvement in symptoms at higher doses. The Beta-blocker Evaluation of Survival Trial (BEST trial) evaluated a patient population with more advanced heart failure than the patients evaluated in successful trials with high doses of the β$_1$-selective agents bisoprolol (Cardiac Insufficiency Bisoprolol Study II [CIBIS-II])[9] and metoprolol succinate (Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure [MERIT-HF]).[10] The BEST trial[12] found that the group of patients with New York Heart Association (NYHA) functional class III heart failure benefited from bucindolol, whereas patients in NYHA functional class IV did not benefit and actually appeared to be harmed.[11] Another subgroup that appeared not to benefit was African Americans. Subsequent detailed examination of the discordant results in patients in the BEST trial has been able to relate adverse outcomes to excessive reduction in circulating levels of norepinephrine, to which African Americans may be especially susceptible.

Sympathetic activation contributes to increases in impedance and exacerbates salt and water retention.

The reduction in circulating levels of plasma norepinephrine following the use of β-adrenergic blocking drugs in patients with heart failure is a composite of the reduction in sympathetic activity which results from long-term improvement in myocardial contractility and the direct effects of specific drug on norepinephrine release and the tendency for acute loss of hemodynamic support to increase sympathetic activity. Thus propranolol (still contraindicated in heart failure), bucindolol, and carvedilol will directly reduce norepinephrine release from adrenergic nerve terminals. Carvedilol and bucindolol minimize any initial fall in contractility support by also producing vasodilation, reversing the effect of β$_2$ adrenoreceptor blockade in the peripheral circulation. Carvedilol and bucindolol do not have the same relative affinity for β$_1$, β$_2$, and α-receptors. The

Table 3
COPERNICUS Patient Population

- The trial recruited 2289 patients with symptoms of heart failure at rest or minimal exertion with a left ventricular ejection fraction below 25% despite diuretics and an angiotensin-converting enzyme inhibitor (with or without digitalis).
- Diuretics were optimized to achieve euvolemia. No need for intensive care and no treatment with IV inotropic or IV vasodilator therapy within 4 days.
- Patients were randomized to placebo or carvedilol (1:1) (target dose 25 mg b.i.d.) up to 29 months.

Table 4
COPERNICUS Principle Exclusion Criteria

Systolic blood pressure	< 85 mmHg
Heart rate	< 68 beats/minute
Serum creatinine	≥ 2.8 mg/dL
Or an increase in serum creatinine	> 0.5 mg/dL
Or a change in body weight	> 1.5 kg within 3–14 days

results of the COPERNICUS trial, which demonstrated a consistent survival benefit in all the patient groups with advanced heart failure, provides the best evidence that the specific properties of the β-adrenergic blocking drug being used to treat heart failure are important and may be especially important in advanced heart failure.

The Carvedilol Prospective Randomized Cumulative Survival Trial

The COPERNICUS trial established that patients with advanced heart failure can benefit substantially from treatment with a β-adrenergic blocking drug.[6] The trial randomized to carvedilol or placebo 2289 patients with symptoms at rest or minimal activity. All the patients had received treatment with an angiotensin-converting enzyme (ACE) inhibitor for at least 2 months prior to determination of eligibility into the trial based on persistent severe refractory symptoms. Patients who were hospitalized qualified for the trial, but patients had to have been discharged from intensive care units and could not have received intravenous inotropic or vasodilator therapy for at least 4 days. Patients who were still receiving intravenous diuretics could be included in the trial. An attempt was made to ensure optimal fluid status before randomization, but patients with a degree of residual fluid retention could be recruited.

Table 3 shows the characteristics of the patients included in the COPERNICUS trial. Patients with a systolic blood pressure above 85 mmHg could be included, as could patients whose heart rate was greater than 68 beats per minute. Table 4 shows the clinical parameters that excluded patients from the trial.

The trial was discontinued on the advice of an independent data monitoring board after predetermined criteria for stopping the trial had been met. The placebo group (largely receiving ACE inhibition therapy) had an annualized mortality of 18.5%

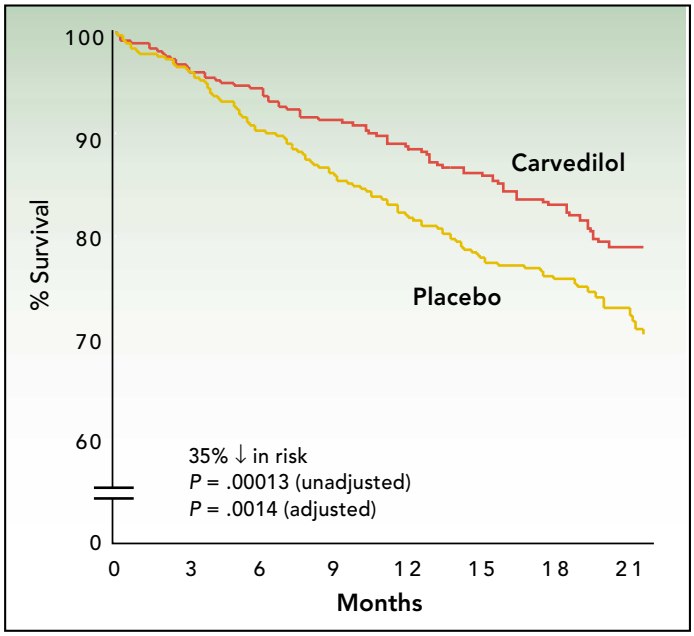

Figure 2. *COPERNICUS all-cause mortality. Data from Packer et al.*[6]

(see Figure 2), which was higher than that observed in the placebo group in the BEST trial and considerably higher than the approximately 10% annual mortality observed in the earlier "positive" U.S. Carvedilol, CIBIS-II, and MERIT-HF trials (see Table 5).

Patients randomized to carvedilol were 35% less likely to die; hospitalization risk was also reduced substantially, with a 20% reduction in all-cause hospitalization and a 33% reduction in hospitalization for heart failure. The drug was well tolerated, and more of those patients withdrawn during double-blind therapy were subsequently found to be randomized to placebo than were withdrawn from the carvedilol group.

It was possible to identify a particular high-risk group of patients within the COPERNICUS trial based on the observed placebo mortality of various subgroups within the higher placebo mortality. The characteristics of these high-risk patients are shown in Table 5. The high-risk group consisted of about a third of the patients in the trial and experienced approximately half the deaths. Even in this group, carvedilol was effective and well tolerated. No demographic subgroup was identified in the COPERNICUS trial that appeared to respond differently from the entire trial population. Tables 6 and 7 show the response in patient groups defined by their blood pressure and heart rate at entry into the trial.

Conclusions

Patients with advanced heart failure can respond favorably to treatment with β-adrenergic blocking drugs. Clinically significant substantial reductions in the risk of dying or of being hospitalized were achieved with carvedilol in the COPERNICUS trial, a unique finding that was not

Table 5
COPERNICUS High-Risk Subgroups

Primary Endpoint—All Patients*

	Placebo	Carvedilol	Hazard Ratio	Log-Rank *P*-Value†
All-Cause Mortality§	190/1133 (18.5%)	130/1156 (11.4%)	0.65 (0.52, 0.81)	0.00014

Patients with Annual Placebo Mortality Rates above 23%‡

	Placebo	Carvedilol	Hazard Ratio	95% CI
All-Cause Mortality	103/460 (25.2%)	64/462 (14.6%)	0.58	(0.43, 0.80)

*No patient was lost to follow-up
†Adjusted *P* = .0014
‡Post-hoc analysis
§Annualized

Table 6
COPERNICUS Systolic Blood Pressure Subgroups

Systolic Blood Pressure Subgroups

	Hazard Ratio (Mortality)	Hazard Ratio (Death + Hospitalization)
85–95 mmHg	0.77	0.75
96–105 mmHg	0.61	0.68
106–115 mmHg	0.64	0.78
116–125 mmHg	0.61	0.65
>125 mmHg	0.60	0.85

Table 7
COPERNICUS Heart Rate Subgroups

	Hazard Ratio (Mortality)	Hazard Ratio (Death + Hospitalization)
68–70 beats/min	0.38	0.70
70–79 beats/min	0.78	0.86
80–89 beats/min	0.83	0.83
90–99 beats/min	0.57	0.59
≥100 beats/min	0.34	0.59

observed when the β-adrenergic blocking drug bucindolol was evaluated in a similar group of patients with only a slightly lower placebo mortality in the BEST trial. Similar results might have been achieved with the β_1-selective agents bisoprolol or metoprolol succinate in a similar group of patients where the placebo mortality was considerably higher than the CIBIS-II and MERIT trials, respectively. This has been suggested in a retrospective subgroup analysis of the MERIT-HF trial, but β_1-selective agents have not been evaluated prospectively in any randomized trial in a patient population with more advanced disease.[13] Patient groups do exist with an even worse prognosis than those recruited into the COPERNICUS trial and have recently been classified as stage D heart failure "refractory to medical therapy" within the new AHA/ACC December 2001 heart failure guidelines.

In the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial, patients in a critically ill group treated with optimal medical therapy all died within 2 years, and the reported life expectancy for patients discharged on intravenous inotropic therapy is especially poor, approaching a 50% 3-to-6-month mortality.[14] These patient groups have not been shown to benefit from any β-adrenergic blocking drugs, but the COPERNICUS trial suggests that if a patient is able to tolerate carvedilol, outcome and quality of life will be improved. In fact the potential risk from not receiving β-adrenergic blocking drugs in advanced heart failure greatly exceeds the potential for harm. The COPERNICUS trial provides evidence that if therapy with a β-adrenergic blocking drug is delayed, some patients are likely to die who might have benefited from carvedilol. Optimal management of all patients with advanced heart failure will include the routine administration of an effective β-adrenergic blocking drug to all patients except those with specific contraindications such as asthma or those at a stage of their disease where the ability to avoid secondary organ failure from low cardiac output or overt cardiogenic shock after weaning from inotropic agents has not been established. ■

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Main Points

- In heart failure, the autoregulation that normally acts to augment sympathetic activity becomes deranged, resulting in chronic and persistent activation of the sympathetic nervous system.
- Sympathetic activation contributes to increases in impedance and exacerbates salt and water retention through vasoconstrictor actions on the circulation and direct effects on the kidneys.
- In mild heart failure, a mild, barely detectable, initial fall in contractility is rapidly reversed by the long-term improvement in contractility and sustained improvement in hemodynamics as a response to β-blockers; early studies suggested a possible diminution of benefit as the disease severity became more advanced.
- Drugs should be introduced at low doses and gradually uptitrated and drugs with vasoconstrictor properties (such as the nonselective, nonvasodilating agent propranolol) should be avoided.
- Successful antiadrenergic therapy in heart failure has been confined to drugs that act as competitive inhibitors of β-adrenergic receptors, and only β-adrenergic blocking drugs have been shown to improve survival in randomized trials.
- The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial established that patients with advanced heart failure can benefit substantially from treatment with a β-adrenergic blocking drug.
- Optimal management of all patients with advanced heart failure should include routine administration of an effective β-adrenergic blocking drug to all patients except those with specific contraindications.

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