Bucindolol reduced mortality and hospitalization related to cardiovascular causes in advanced chronic heart failure

The Beta-Blocker Evaluation of Survival Trial Investigators. **A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure.** N Engl J Med. 2001 May 31;344:1659-67.

QUESTION

In patients with advanced chronic heart failure, does bucindolol reduce all-cause mortality, cardiovascular mortality, and hospitalization for chronic heart failure?

DESIGN

Randomized (allocation concealed*), blinded (clinicians and patients),* placebo-controlled trial with mean follow-up of 2 years (Beta-Blocker Evaluation of Survival Trial [BEST]).

SETTING

90 clinical sites in the United States and Canada.

PATIENTS

2708 patients (mean age 60 y, 78% men). Inclusion criteria were New York Heart Association (NYHA) class III or IV chronic heart failure caused by primary or secondary dilated cardiomypathy; left ventricular ejection fraction ≤ 35%; treatment with optimal medical therapy, including angiotensin-converting enzyme inhibitors for ≥ 1 month; and ≥ 18 years of age. Exclusion criteria included reversible heart failure; uncorrected primary valvular disease; active myocarditis; recent myocardial infarction or revascularization; unstable angina; heart rate < 50 beats/min; or serious concomitant illness.

INTERVENTION

Patients were allocated to bucindolol, 3 mg twice/d for 1 week, which was then titrated gradually to a maximum dose of 100 mg twice/d (n = 1354) or to placebo (n = 1354).

MAIN OUTCOME MEASURES

All-cause mortality, cardiovascular mortality, and hospitalization related to chronic heart failure.

MAIN RESULTS

Analysis was by intention to treat. The groups did not differ for all-cause mortality (adjusted P = 0.13) (Table). Patients in the bucindolol group had a lower rate of cardiovascular mortality (P = 0.04) and hospitalization for chronic heart failure (P < 0.001) than did patients in the placebo group (Table).

CONCLUSIONS

In patients with advanced chronic heart failure, bucindolol did not reduce all-cause mortality; however, mortality from cardiovascular causes and hospitalization for chronic heart failure were reduced.

Sources of funding: U.S. National Heart, Lung, and Blood Institute; Department of Veterans Affairs Cooperative Studies Program; Incara Pharmaceuticals (drugs).

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*See Glossary.

Bucindolol vs placebo for advanced chronic heart failure (CHF)†

Outcomes at mean 2 y	Bucindolol	Placebo	RRR (95% CI)	NNT (CI)
All-cause mortality	30%	33%	8% (–2 to 18)	Not significant
Mortality from cardiovascular diseases	25%	29%	12% (0.4 to 22)	29 (15 to 790)
Hospitalization for CHF	35%	42%	16% (8 to 24)	15 (10 to 32)

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

COMMENTARY

Do β-blockers improve morbidity and mortality in patients with heart failure? 3 large trials have shown the benefits of bisoprolol (1), carvedilol (2), and metoprolol (3) on morbidity and mortality among patients with NYHA class II or III heart failure and have had important implications for how patients with mild-to-moderate heart failure are treated. On the basis of these studies, it has now become standard practice to treat such patients with one of these β-blockers. Whether patients with severe heart failure would also benefit from β-blockade has been unanswered. Patients with severe heart failure have the highest sympathetic outflow and theoretically may benefit most from β-blockade. These patients also have the least inotropic reserve and thus are most susceptible to decompensation when treated with β-blockade.

These 2 studies (BEST and COPERNICUS) have provided important data that allow us to assess the benefit of β-blockers in patients with severe heart failure. What is certain is that the benefit of β-blockers is largely dependent on the type of patients who receive them. Unfortunately, assessing the value of β-blockers in patients with severe heart failure is problematic. First, measuring and comparing severity is difficult. The NYHA functional classification is a useful guide, but as pointed out by Braunwald (4), it is subjective and thus inherently imprecise. An alternative way of comparing the severity of heart failure among patients in different trials is to use placebo mortality rates. Subsets of patients in whom the annual placebo mortality rate is high (e.g., 20%) are said to have very severe heart failure. This measure also has its limitations because it does not reflect only mortality caused by heart failure and it does not include any measure of severity of symptoms, frequency of hospitalization, or quality of life.

We are left with 2 well-designed studies, only one of which shows a substantial benefit of β-blocker therapy on mortality in patients with severe heart failure. These differing conclusions may have resulted from study populations that were different or from differences in the pharmacologic actions of bucindolol and carvedilol. The benefits of carvedilol may be related to its unique α-adrenergic, antioxidant, or antiendothelin effects.

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Carvedilol reduced mortality and hospitalization in severe chronic heart failure

Packer M, Coats AJ, Fowler MB, et al., for the Carvedilol Prospective Randomized Cumulative Survival Study Group. **Effect of carvedilol on survival in severe chronic heart failure.** N Engl J Med. 2001 May 31;344:1651-8.

QUESTION

In patients with severe chronic heart failure, does carvedilol, a β-blocker, reduce mortality and hospitalization?

DESIGN

Randomized {allocation concealed*}†, blinded (patients and clinicians),* placebo-controlled trial with mean follow-up of 10.4 months (Carvedilol Prospective Randomized Cumulative Survival Study [COPERNICUS]).

SETTING

334 centers in 21 countries.

PATIENTS

2289 patients (mean age 63 y, 80% men). Inclusion criteria were dyspnea or fatigue at rest or on minimal exertion for ≥ 2 months; left ventricular ejection fraction ≤ 25%; absence of rales and ascites; minimal or no peripheral edema; not hospitalized for intensive care or continued inpatient care; and no recent intravenous inotropic agents or vasodilators. Exclusion criteria included chronic heart failure caused by uncorrected primary valvular disease or reversible cardiomyopathy; recent coronary revascularization, acute myocardial or cerebral ischemic event, or ventricular tachycardia or fibrillation; systolic blood pressure < 85 mm Hg; heart rate < 68 beats/min; or serum creatinine level > 2.8 mg/dL. Follow-up was 100%.

INTERVENTION

Patients were allocated to carvedilol, 3.125 g twice/d for 2 weeks, which was then titrated to 25 mg twice/d if tolerated (n = 1156) or to placebo (n = 1133). Both groups received usual medications for chronic heart failure.

MAIN OUTCOME MEASURES

Mortality and combined risk for death or hospitalization for any reason.

MAIN RESULTS

Analysis was by intention to treat and used Kaplan–Meier survival curves. The cumulative risk for death at 1 year was lower in the carvedilol group than the placebo group (adjusted P = 0.001) (Table). The risk for combined death or hospitalization in the carvedilol group was lower than that in the placebo group (P < 0.001) (Table).

CONCLUSION

Carvedilol reduced mortality and the combined risk for death or hospitalization in patients with severe chronic heart failure.

Sources of funding: Roche Pharmaceuticals and Glaxo SmithKline.

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*See Glossary.

†Information provided by author.

Carvedilol vs placebo for severe chronic heart failure‡

Outcomes at 1 y	Carvedilol	Placebo	RRR (95% CI)	NNT (CI)
Risk for death	11%	19%	35% (19 to 48)	15 (10 to 25)
Combined risk for death or hospitalization	42%	53%	24% (13 to 33)	10 (7 to 15)

‡Abbreviations defined in Glossary; NNT and CI calculated from data in article.

COMMENTARY *(continued from page 84)*

The positive results from the BEST study—namely, the decrease in mortality specific to cardiovascular causes and the decrease in overall mortality among nonblack patients—should not be ignored. The results of previous studies and these 2 new investigations, coupled with our increasing understanding of the role of the adrenergic nervous system in heart failure, can be used to derive a rational set of recommendations. First, patients with mild or moderate heart failure should receive β-blockers. As heart failure becomes more severe in these same patients, β-blockade must strike a delicate balance so that it is forceful enough to block the adverse effects of the sympathetic nervous system but gentle enough to maintain any positive role this system plays in survival. For this reason, patients receiving β-blockers who develop progressive heart failure must be closely monitored. When patients with mild-to-moderate chronic heart failure who are treated with other β-blockers progress to severe heart failure, switching them to carvedilol should be considered. Additional evidence is needed before more widespread use of β-blockers in patients with severe heart failure can be recommended. Because the type of β-blocker may be very important, a trial directly comparing bucindolol and carvedilol would provide valuable evidence.

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References

1. The Cardiac Insufficiency Bisoprolol Study II (CIBIS II): a randomised trial. Lancet. 1999;353:9-13.
2. **Packer M, Bristow MR, Cohn JN, et al.** The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. N Engl J Med. 1996;334:1349-55.
3. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet. 1999;353:2001-7.
4. **Braunwald E.** Expanding indications for beta-blockers in heart failure. N Engl J Med. 2001;344:1711-2.

