Bisoprolol reduced all-cause mortality, cardiovascular mortality, and hospitalization in CHF

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The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet. 1999;353:9-13.[PubMed ID: 10023943]

Question

Does bisoprolol reduce all-cause mortality in patients with chronic heart failure (CHF)?

Design

Randomized, double-blind, placebo-controlled trial with 2 planned interim analyses (Cardiac Insufficiency Bisoprolol Study II [CIBIS-II]). Mean follow-up was 1.3 years.

Setting

274 hospitals in 18 countries in western and eastern Europe.

Patients

2647 ambulatory patients (mean age 61 y, 81% men) with clinically stable CHF (New York Heart Association [NYHA] class III or IV). Inclusion criteria were age 18 to 80 years, left ventricular ejection fraction ≤35%, and use of a diuretic and an angiotensin-converting enzyme (ACE) inhibitor. Exclusion criteria were uncontrolled hypertension, cardiac surgery in the past 6 months, first-degree or greater heart block without a pacemaker, resting heart rate 60 beats/min, systolic blood pressure < 100 mm Hg, renal failure, reversible obstructive lung disease, or use of or need for β-adrenoceptor blockers.

Intervention

1327 patients were allocated to bisoprolol, a selective β-adrenoceptor blocker, at a starting dose of 1.25 mg/d that was increased to 10 mg/d as tolerated. 1320 patients were allocated to placebo. Analysis included all patients in an intention-to-treat analysis.

Main outcome measures

All-cause mortality. Secondary outcomes were all-cause hospitalization, cardiovascular (CV) mortality, CV mortality plus CV hospitalization, and premature treatment withdrawal.

Main results

The study was stopped early because interim analysis showed a treatment benefit. Patients in the bisoprolol group had lower rates of all-cause mortality ($P < 0.001$), all-cause hospitalization ($P < 0.001$), CV mortality ($P = 0.005$), and combined CV mortality or CV hospitalization ($P < 0.001$) than did patients in the placebo group (Table). Other analyses showed that patients in the bisoprolol group also had lower rates of sudden death (4% vs 6%, $P = 0.001$), unknown cause of death (2% vs 4%, $P = 0.001$), and hospitalization for worsening CHF (12% vs 18%, $P < 0.001$).

Conclusions

Patients with chronic heart failure who received bisoprolol had lower rates of all-cause mortality, cardiovascular mortality, and hospitalization.

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Bisoprolol vs placebo for chronic heart failure at mean follow-up of 1.3 y*

Outcomes	Bisoprolol	Placebo	RRR (95% CI)	NNT (CI)
All-cause mortality	11.7%	17.3%	31.9% (18 to 44)	18 (12 to 35)
All-cause hospitalization	33.2%	38.9%	14.8% (6 to 23)	17 (11 to 47)
CV mortality	9.0%	2.2%	26.5% (8 to 41)	31 (18 to 112)
CV mortality or CV hospitalization	29.2%	35.1%	16.6% (7 to 25)	17 (11 to 44)

*CV = cardiovascular. Other abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

Commentary

Many years have passed since the first study showed that β-blockers might have a beneficial effect in patients with CHF (1). CIBIS-II, the largest trial to date of β-blockers in patients with moderate-to-severe symptomatic CHF, had a risk reduction consistent with that seen in meta-analyses of other trials (2). Bisoprolol was well tolerated when the dose was titrated up over several months: Most patients reached either the target dose of 10.0 mg or a dose of 7.5 mg, and the number of permanent treatment withdrawals was similar for patients treated with β-blockers and those receiving placebo (15% in each group). Because no run-in period was included, the patients recruited for this study were not selected for their tolerance of bisoprolol, which further supports the general tolerability of this drug. A subgroup analysis done by cause and severity of CHF at baseline showed that the mortality reduction did not differ between treatment and control groups for these categories. The patients in this trial were at moderately high risk (approximately 80% were NYHA class III at baseline, and the placebo group had an annual mortality of 13.2%). Finally, these results show incremental benefits of β-blocker therapy over accepted drugs for CHF because > 90% of patients were receiving ACE inhibitors.

This large, well-designed trial supports the addition of β-blockers to standard therapy with a diuretic and an ACE inhibitor in patients with stable, moderately severe, and severe CHF caused by systolic dysfunction.

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