Carvedilol reduced mortality and hospital admission in severe chronic heart failure, regardless of pretreatment systolic BP

Rouleau JL, Roecker EB, Tendera M, *et al.* Influence of pretreatment systolic blood pressure on the effect of carvedilol in patients with severe chronic heart failure: the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study. *J Am Coll Cardiol* 2004;**43**:1423–9.

Clinical impact ratings IM/Ambulatory care ★★★★★★★ Internal medicine ★★★★★★★ Cardiology ★★★★★★☆

Q How does pretreatment systolic blood pressure (SBP) affect the efficacy and safety of carvedilol in patients with severe chronic heart failure (HF)?

METHODS

Design: randomised controlled trial (Carvedilol Prospective Randomized Cumulative Survival [COPERNICUS] study).

Allocation: concealed.*

Blinding: blinded (patients and outcome assessors).*

Follow up period: mean 10.4 months at early termination of study.

Setting: 334 centres in 21 countries.

Patients: 2289 patients (mean age 63 y, 80% men) with severe chronic HF because of ischaemic or non-ischaemic cardiomyopathy; ⩾2 months of dyspnoea or fatigue at rest or on minimal exertion; left ventricular ejection fraction <25%; and SBP >85 mm Hg. Exclusion criteria: correctable cause of HF; heart transplant; severe primary pulmonary, renal, or hepatic disease; contraindications to β blockers; major cardiac event within 2 months; use of α adrenergic blockers, calcium channel blockers, or class I antiarrhythmic drugs within 4 weeks; heart rate <68 beats/minute, serum creatinine concentration >2.8 mg/dl or an increase of >0.5 mg/dl, serum potassium <3.5 or >5.2 mmol/l. Patients were retrospectively grouped according to pretreatment SBP: 85–95 mm Hg (n = 132), 96–105 mm Hg (n = 264), 106–115 mm Hg (n = 468), 116–125 mm Hg (n = 472), or >125 mm Hg (n = 953).

Intervention: in addition to usual medication for HF, oral carvedilol, initial dose 3.125 mg twice daily for 2 weeks, which was increased as tolerated at 2 week intervals to 6.25 mg, 12.5 mg, and finally 25 mg twice daily (n = 1156), or matching placebo (n = 1133).

Outcomes: included all cause mortality; combined death or hospital admission for HF; combined death or cardiovascular admission; combined death or hospital admission; and adverse events.

Patient follow up: 100% (intention to treat analysis).

*See glossary.

MAIN RESULTS

Overall, carvedilol reduced all cause mortality by 35%, combined death or cardiovascular admission by 27%, combined death or admission for HF by 31%, and combined death or admission for any reason by 24% (all p<0.001). Regardless of treatment, the lower the pretreatment SBP, the higher the risk of a major clinical event. However, the relative magnitude of treatment benefits did not vary as a function of SBP (all interaction, p>0.1).

More patients in the carvedilol group than in the placebo group reported dizziness (24% *v* 17%, {p<0.0001}*), hypotension (15% *v* 9%, {p<0.0001*}), syncope (8% *v* 5%, {p = 0.0045}*), and bradycardia (12% *v* 3%, {p<0.0001}*), whereas fewer patients reported HF (28% *v* 34%, {p = 0.002}*), to a similar extent in each BP subgroup. The risk of a serious adverse event increased as pretreatment BP decreased (p<0.001). However, patients in the carvedilol group were less likely to have a serious adverse event than those who received placebo (39% *v* 46%, p = 0.002). This benefit increased as pretreatment SBP decreased (interaction p = 0.03).

CONCLUSION

In patients with severe chronic heart failure, carvedilol reduced the risk of all cause mortality and combined mortality and general and cause specific hospital admission regardless of pretreatment systolic blood pressure.

*Calculated from data in article.

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Commentary

The COPERNICUS study was designed to examine the effect of carvedilol on mortality in patients with severe HF and a left ventricular ejection fraction <25%. Clearly, with a 35% reduction in mortality, COPERNICUS proved the benefits of carvedilol in patients with severe HF having symptoms at rest or with minimal exertion. However, some clinicians may be reluctant to initiate carvedilol in patients with advanced HF with relative hypotension below a SBP of 110 mm Hg. Rouleau *et al* help to alleviate concerns regarding use of β blockers, specifically carvedilol, in patients with severe HF and low BP. In their retrospective subgroup analysis of COPERNICUS, the authors showed that patients who had the lowest BP, and thus the highest risk of death or morbidities, derived the greatest absolute benefit from treatment with carvedilol. Interestingly, these patients also have other characteristics supporting their advanced stage of disease, with a lower ejection fraction, higher creatinine concentrations, lower sodium concentrations, and a higher rate of spironolacatone use. Since this publication, others have addressed similar concerns of the adverse effects of β blockers by performing a meta-analysis of 9 trials (>14 000 patients) to reach the same conclusion that adverse effects, including hypotension, are low, whereas the overall benefits are quite large.[1] However, it is important to remember that patients with the most advanced HF (eg, those with ongoing decompensated HF or those requiring inotropic support) were not included in these studies. Furthermore, patients with SBP ⩽85 mm Hg were excluded from COPERNICUS. Thus, initiation of β blockers is supported once acute issues have resolved, even in patients with relative hypotension. For most patients, it is safe to initiate β blockers before discharge, and evidence suggests that outpatient use of β blockers is higher if started before discharge.[2]

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1 Ko DT, Hebert PR, Coffey CS, *et al.* Adverse effects of beta-blocker therapy for patients with heart failure: a quantitative overview of randomized trials. *Arch Intern Med* 2004;**164**:1389–94.
2 Gattis WA, O'Connor CM, Gallup DS, *et al.* Predischarge initiation of carvedilol in patients hospitalized for decompensated heart failure: results of the Initiation Management Predischarge: Process for Assessment of Carvedilol Therapy in Heart Failure (IMPACT-HF) trial. *J Am Coll Cardiol* 2004;**43**:1534–41.