

THERAPEUTICS

# Review: $\beta$ -blockers reduce mortality and therapy withdrawal in heart failure but increase dizziness and bradycardia

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.

**QUESTION**

In patients with heart failure (HF) with systolic dysfunction, what are the risks associated with  $\beta$ -blocker therapy?

**METHODS**

**Data sources:** Studies were identified by searching MEDLINE (1966 to 2002) and bibliographies of relevant articles.

**Study selection and assessment:** Studies were selected if they were randomized controlled trials (RCTs) that used noncrossover designs, compared  $\beta$ -blocker therapy with placebo in patients with HF with left ventricular systolic dysfunction, enrolled  $\geq 100$  patients in each treatment group, had  $\geq 6$  months of follow-up, and reported adverse effects.

**Outcomes:** All-cause therapy withdrawal, all-cause mortality, HF hospitalization, worsening HF, hypotension, dizziness, bradycardia, and fatigue.

**MAIN RESULTS**

9 RCTs (14 594 patients, mean age range 49 to 67 y) with mean follow-up 6 to 24 months were included. Interventions included carvedilol (3 RCTs), metoprolol (3 RCTs), bisoprolol (2 RCTs), and bucindolol (1 RCT). Compared with placebo,  $\beta$ -block-

er therapy reduced the risks for all-cause mortality, HF hospitalization, worsening HF, and all-cause withdrawal of therapy but increased the risks for dizziness and bradycardia; groups did not differ for hypotension or fatigue (Table).

**CONCLUSION**

In patients with heart failure (HF) with systolic dysfunction,  $\beta$ -blocker therapy reduces

the risks for all-cause mortality, HF hospitalization, worsening HF, and all-cause withdrawal of therapy, but is associated with increased risks for dizziness and bradycardia.

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**$\beta$ -blocker therapy vs placebo for heart failure (HF) with systolic dysfunction at mean 6 to 24 months\***

Outcomes	Number of trials (n)	Weighted event rates		RRR (95% CI)	NNT (CI)	NNT/y
		$\beta$ -blocker	Placebo			
All-cause mortality	9 (14 594)	13%	17%	27% (15 to 38)	22 (16 to 39)	30
HF hospitalization	8 (13 478)	17%	23%	26% (17 to 34)	17 (13 to 26)	25
Worsening HF	4 (4439)	26%	34%	17% (2 to 29)	18 (11 to 150)	19
All-cause withdrawal of therapy	9 (14 594)	16%	18%	11% (2 to 19)	51 (30 to 278)	72
				RRI (CI)	NNH (CI)	NNH/y
Dizziness	4 (10 082)	22%	17%	37% (9 to 71)	17 (9 to 67)	17
Bradycardia	7 (13 796)	6%	2%	262% (148 to 428)	22 (14 to 39)	26
Hypotension	7 (13 796)	8%	6%	41% (-4 to 106)	Not significant	91
Fatigue	3 (7793)	24%	22%	4% (-3 to 11)	Not significant	297

\*Abbreviations defined in Glossary; RRR, RRI, NNT, NNH, and CI calculated from data in article using a random-effects model.

**COMMENTARY**

The review by Ko and colleagues of trials of placebo-controlled  $\beta$ -blockers for HF discusses the overall benefits of these agents, which are substantial, in the context of adverse effects, which are minimal, and do not seem to affect therapy withdrawal (except to actually prevent therapy withdrawal). The only criticism of this review is that no quality rating was used for the individual studies. The most relevant quality component would be the use of a systematic method for assessing side effects within each study and whether this affected the differential discovery of adverse events. Without a systematic method, one could imagine potential bias against finding adverse events or side effects, making it possible to underestimate the incidence of side effects. Nevertheless, the fact that patients were less likely to withdraw from other lifesaving therapies when they were receiving a  $\beta$ -blocker shows that this may not be a substantial issue.

Other side effects that might have been attributable to  $\beta$ -blockers not reported in this synthesis include depression and sexual dysfunction. In a previous meta-analysis by these authors, no increased risk for

depressive symptoms was associated with  $\beta$ -blockers, and only a small increased risk for sexual dysfunction or fatigue was seen (1). Thus, it seems quite clear that, in patients with HF with systolic dysfunction, one should not be deterred by the relatively minor side effect profiles of  $\beta$ -blockers (even in patients with chronic obstructive pulmonary disease and diabetes), especially given the survival benefit associated with these agents.

Some lingering questions exist, however. Because the upper age limit was 67 years, how generalizable are these results to older patients who have the largest illness burden from HF and who take more medications with which  $\beta$ -blockers could interact? Are there differential effects of different types of  $\beta$ -blockers? Are all  $\beta$ -blockers equally effective?

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**Reference**

1. Ko DT, Hebert PR, Coffey CS, et al. Beta-blocker therapy and symptoms of depression, fatigue, and sexual dysfunction. JAMA. 2002;288:351-7.