Comparative Effectiveness of β Blockers in Heart Failure

Go AS, Yang J, Gurwitz JH, et al. Comparative effectiveness of different β-adrenergic antagonists on mortality among adults with heart failure in clinical practice. Arch Intern Med 2008;168:2415–21.

Study Overview

Objective. To compare the risk of mortality with different β blockers among a large, contemporary sample of adults with heart failure.

Design. Retrospective review of data from administrative, hospital, outpatient, and pharmacy databases.

Setting and participants. 11,326 patients aged ≥ 18 years hospitalized between 1 January 2001 and 31 December 2003, with a primary discharge diagnosis of heart failure (based on ICD-9-CM codes). Patients were identified from membership lists of Kaiser Permanente of Northern California and Harvard Pilgrim Health Care. Participants were excluded if they had a length of stay < 24 hours, died during index heart failure hospitalization, or had no continuous membership and pharmacy benefit for ≥ 12 months before admission date and ≥ 12 months after discharge or until censoring during first year after discharge. Patients were followed for up to 12 months after discharge.

Main outcome measure. Death within 12 months of discharge from the index hospitalization by β-blocker exposure category. Deaths were ascertained by matching with Social Security Administration Death Master File data, site-specific data sources, and state death files. Exposure to β blockers was defined as the continuation of therapy with prehospitalization β blockers, switching to a different β blocker, or initiation of a new β blocker at discharge or during follow-up and was determined by pharmacy databases. β-blocker categories included atenolol, metoprolol tartrate, carvedilol, other β blockers, and no β blockers.

Main results. Of 11,326 eligible patients, 7976 (70.4%) received β blockers (metoprolol tartrate, 43.2%; atenolol, 38.5%; carvedilol, 11.6%; and other, 6.7%) after discharge. The crude rate (per 100 person-years) of death varied by β-blocker type (carvedilol, 17.7; atenolol, 20.1; metoprolol tartrate, 22.8; other β blockers, 21.9; no β blockers, 37.0). After adjusting for confounders and the propensity to receive carvedilol, the risk of death compared with atenolol was higher for metoprolol tartrate (adjusted hazard ratio [HR], 1.16 [95% confidence interval {CI}, 1.01–1.34]) and no β blockers (HR, 1.63 [95% CI, 1.44–1.84]) but was not significantly different for carvedilol (HR, 1.16 [95% CI, 0.92–1.44]).

Conclusion. In this study of adults with heart failure, 1-year survival after hospitalization was similar in patients receiving atenolol and carvedilol but was slightly worse in patients receiving shorter-acting metoprolol tartrate as compared with atenolol.

Commentary

β Blockers are a mainstay of therapy for heart failure caused by left ventricular systolic dysfunction (LVSD) [1]. Along with angiotensin-converting enzyme (ACE) inhibitors [2], angiotensin receptor blockers [3], and aldosterone antagonists [4], β blockers have been shown to reduce mortality in patients with heart failure caused by LVSD in several randomized controlled trials (RCTs) [5–8]. However, significant gaps remain in understanding which β blockers provide a survival benefit. Only 7 β blockers have been evaluated in RCTs—carvedilol, shorter-acting metoprolol tartrate, longer-acting metoprolol succinate, bisoprolol, nebivolol, xamoterol, and bucindolol. Of these, carvedilol [5], metoprolol succinate [6], bisoprolol [7], and nebivolol [8] have been shown to be superior to placebo in improving survival in patients with heart failure with LVSD. Negative results from trials involving bucindolol [9] and xamoterol [10] argue against a general class effect. The only RCT directly comparing 2 β blockers was the COMET study [11], in which carvedilol was found to be superior to metoprolol tartrate. In particular, no placebo-controlled RCTs have evaluated atenolol or metoprolol tartrate, 2 of the most widely used β blockers, for a survival benefit in patients with heart failure. There is nothing to suggest that these agents would not be beneficial.

In clinical practice, some patients with heart failure continue to be treated with no β blockers or with β blockers not shown to have a survival benefit (ie, non–evidence-based β blockers [EBBBs]). In the absence of RCTs directly comparing these agents, observational studies may help assess their relative effectiveness in treating heart failure. Accumulating data suggest that non-EBBBs may be equivalent to EBBBs on

several measures. Among approximately 386 patients in the OPTIMIZE-HF registry on treatment with non-EBBBs, there was no difference in 30- to 60-day mortality after hospitalization for heart failure [12]. Additionally, a recent observational study [13] showed that adjusted rates of rehospitalization did not vary significantly with atenolol, metoprolol tartrate, or carvedilol. Kramer et al [14] also found that elderly patients with heart failure taking EBBBs had similar 1-year mortality (as compared with those taking non-EBBBs) and had a higher rehospitalization rate.

The study by Go et al adds to the accumulating evidence on the comparative effectiveness of β blockers in heart failure. Compared with atenolol, a small increase (16%) in relative risk of 1-year mortality was found with metoprolol tartrate, but there was no significant difference when compared with carvedilol. Patients not taking β blockers had a 63% increased relative risk of mortality at 1 year. A subgroup analysis of 2929 (25.9%) patients taking digoxin (used as a proxy for LVSD) found no difference in mortality among β blockers and an 85% increased relative risk of mortality in patients not taking a β blocker. A relatively small number of patients (6.7%) taking other β blockers (including longer-acting metoprolol succinate) were grouped into a single category and had mortality rates similar to those taking atenolol or carvedilol.

The results of the study suggest that atenolol and carvedilol are essentially equivalent in providing survival benefit in patients with heart failure. However, this study was not without limitations. Whereas RCTs of β blockers in heart failure have specifically studied patients with reduced LVSD, the study by Go et al provides no information on LVSD and uses digoxin as a proxy for LVSD in subgroup analysis. However, patients with LVSD do not always take digoxin, which has only been shown to decrease hospitalizations in patients with LVSD [15], and digoxin may be prescribed for conditions other than heart failure, such as atrial fibrillation and atrial flutter. This confounds the subgroup analysis suggesting equivalence of β blockers in reducing mortality. To date, the benefit of β blockers in patients with preserved left ventricular systolic function remains unclear.

Additionally, there is confounding by indication. Atenolol is commonly prescribed for hypertension, whereas carvedilol is more commonly prescribed for heart failure. Indeed, the study found that 66.7% of patients taking atenolol had hypertension as compared with only 43.7% of patients taking carvedilol. Patients on carvedilol were more likely to be taking ACE inhibitors, angiotensin receptor blockers, digoxin, aldosterone antagonists, and hydralazine at baseline than patients on other β blockers. It is possible that patients taking carvedilol were managed by cardiologists more familiar with heart failure management guidelines than generalists prescribing atenolol. It is also possible that

patients taking carvedilol had more LVSD than those taking other β blockers, thus necessitating the use of a conglomerate of heart failure medications. The study does not provide relevant information to draw such conclusions.

The medication profiles of patients taking carvedilol makes one question if they were sicker with more LVSD, thus resulting in a higher mortality rate. However, baseline characteristics suggest that patients taking carvedilol were (on some measures) less sick than those on other β blockers, with a mean age 6.1 years younger than those on atenolol and with lower rates of prior coronary disease and stroke. On the other hand, only 33.3% of patients taking carvedilol were women, whereas the percentage of women taking atenolol, metoprolol, and other β blockers was around 50%. Studies have shown that women are less likely to receive appropriate therapy for heart failure [16]. Indeed, the crude death rate was lowest for carvedilol, and atenolol was not far behind. Carvedilol and atenolol were shown to be equally effective only after adjusting for the above factors and other characteristics. This finding highlights that great care must be taken to control for confounding variables in comparative effectiveness studies derived from observational data, as small differences may appear or disappear depending on the statistical analysis.

There is evidence that poor compliance is associated with higher rehospitalization rates in patients with heart failure [17]. The present study does not provide data on compliance or side effects associated with various β blockers. In other studies, carvedilol has been associated with fewer side effects and better glycemic profiles [18]. The value of a comparative effectiveness study is that it can evaluate the cumulative effects of such "real world" factors.

Finally, relatively few patients in the study were taking metoprolol succinate, which has been shown in RCTs to improve survival [6]. Patients taking this medication were grouped with patients taking other β blockers, and conclusions cannot be drawn from the data provided. Further studies, perhaps involving more recent or larger cohorts, are needed to evaluate the comparative effectiveness of metoprolol succinate and other EBBBs as compared with non-EBBBs.

Applications for Clinical Practice

Selecting a β blocker for a patient with heart failure can be challenging. For patients with systolic heart failure, current guidelines [1] recommend using 1 of several EBBBs proven to reduce mortality in RCTs. However, if a patient is already on a β blocker for a different indication (eg, hypertension), it may be tempting to continue the same β blocker rather than switch medications. The present study further suggests that some non-EBBBs may be equivalent to EBBBs in providing a survival benefit; a definitive randomized trial addressing

this question is unlikely. Finally, although the present study suggests a benefit of β blockers for patients with diastolic heart failure, additional evidence is required in this regard.

—Review by Rishikesh P. Dalal, MD (New York University School of Medicine, New York, NY), and Nirav R. Shah, MD, MPH

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