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Beta-Blockers for Primary Prevention of Heart Failure in Patients With Hypertension

Insights From a Meta-Analysis

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Objectives This study sought to evaluate the efficacy of beta-blockers (BBs) for primary prevention of heart failure (HF) in patients with hypertension.

Background The American College of Cardiology/American Heart Association staging for HF classifies patients with hypertension as stage A HF, for which BBs are a treatment option. However, the evidence to support this is unknown.

Methods We conducted a MEDLINE/EMBASE/CENTRAL search of randomized controlled trials that evaluated BB as first-line therapy for hypertension with follow-up for at least 1 year and with data on new-onset HF. The primary outcome was new-onset HF. Secondary outcomes were all-cause mortality, cardiovascular mortality, myocardial infarction, and stroke.

Results Among the 12 randomized controlled trials, which evaluated 112,177 patients with hypertension, BBs reduced blood pressure by 12.6/6.1 mm Hg when compared with placebo, resulting in a 23% (trend) reduction in HF risk ($p = 0.055$). When compared with other agents, the antihypertensive efficacy of BBs was comparable, which resulted in similar but no incremental benefit for HF risk reduction in the overall cohort (risk ratio: 1.00; 95% confidence interval: 0.92 to 1.08), in the elderly (≥60 years) or in the young (<60 years). Analyses of secondary outcomes showed that BBs confirmed similar but no incremental benefit for the outcomes of all-cause mortality, cardiovascular mortality, and myocardial infarction but increased stroke risk by 19% in the elderly.

Conclusions In hypertensive patients, primary prevention of HF is strongly dependent on blood pressure reduction. When compared with other antihypertensive agents, there was similar but no incremental benefit of BBs for the prevention of HF. However, given the increased risk of stroke in the elderly, BBs should not be considered as first-line agents for prevention of HF. (J Am Coll Cardiol 2008;52:1062–72) © 2008 by the American College of Cardiology Foundation

Chronic heart failure (HF) is the only major cardiovascular disease increasing in both incidence and prevalence, with 550,000 new cases diagnosed every year, affecting both genders equally (1). The prevalence in the U.S. is increasing, with 50 HF patients per 1,000 people over the age of 65 years (1). The increase in the incidence and prevalence of HF seem to parallel the increase in incidence and prevalence of hypertension. The Framingham study has shown that hypertension has the greatest influence on the risk of future HF, accounting for 39% of HF in men and 59% in women (2,3). It confers a 2-fold higher risk of HF, carrying the highest population-attributable risk among all risk factors, and this risk increases in a graded continuous fashion with increase in blood pressure (2–4). More than 90% of patients

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with HF have hypertension (3). The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines committee has recognized this important risk factor; patients with hypertension are classified as stage A HF (those with risk factors for HF), and primary prevention of overt HF (stage C HF) is important in this cohort (5).

Although hypertension is an important risk factor, its treatment results in a 49% to 81% reduction in the risk of developing HF (6). The ACC/AHA guidelines (5) state

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that in patients at high risk for developing HF, systolic and diastolic blood pressure should be controlled in accordance with contemporary guidelines, and beta-blockers (BBs) are an option based on the 7th report of the Joint National Committee on hypertension (7). Although BBs are a reasonable option for patients with stage B HF (asymptomatic left ventricular dysfunction) caused by a prior myocardial infarction, its role in patients with stage B HF caused by left ventricular hypertrophy or in hypertensive patients with stage A HF is not well defined.

Messerli et al. (8) had documented nearly a decade earlier that although blood pressure was lowered by BBs, these drugs were ineffective in preventing coronary artery disease and cardiovascular and all-cause mortality (odds ratio: 1.01, 0.98, and 1.05, respectively) in patients with hypertension. Other meta-analyses (9,10) and reviews (11) have noted similar results, resulting in withdrawal of endorsement for these medications as first-line therapy for hypertension by major national and international guidelines (12,13). Despite this, they remain the fourth-largest selling drug class in the U.S. (14). In a recent survey (15) in which physicians were asked, "Which of the following class of drugs have been proven to reduce the risk of stroke in hypertensive patients?" BBs were by far considered the most effective class. Similarly, when asked, "Which of the following classes of drugs have been proven to reduce mortality in hypertensive patients?" BBs were rated highest. These perceptions or misperceptions are unfortunate and probably occur because physicians extrapolate their cardioprotective effects in HF and myocardial infarction to patients with uncomplicated hypertension (16).

The beneficial effect of BBs for primary prevention of HF in patients with hypertension is unknown. The objective of the present analysis was to evaluate the efficacy of BBs for prevention of progression to overt HF in patients with hypertension.

Methods

Search strategy. We conducted a MEDLINE/EMBASE/CENTRAL search of studies using the terms: "beta adrenergic blockers," "adrenergic beta antagonist," "beta-blockers," and "hypertension." We limited our search to studies in human subjects published in journals from 1966 to May 2008. We checked the reference lists of reviewed articles, prior meta-analyses, and original studies identified by the electronic search to find other potentially eligible studies. Trials that were only in abstract form without an article published were not considered for this analysis.

Eligible trials had to fulfill the following criteria to be included in this analysis: 1) randomized controlled trials (RCTs) to be included if they enrolled adult hypertensive patients, both genders, with or without other cardiovascular risk factors, with or without comorbidities but with no established HF; 2) RCTs to be included if they evaluated BBs as first line monotherapy both as intervention (i.e., vs. placebo) or as comparator (i.e., vs. other antihypertensive drugs); 3) follow-up of at least 1 year; and 4) RCTs to be included if they assessed HF as an outcome, being primary or secondary, predefined or analyzed post hoc.

Abbreviations and Acronyms

ACC = American College of Cardiology
ACEI = angiotensin-converting enzyme inhibitor
AHA = American Heart Association
ARB = angiotensin receptor blocker
BB = beta-blocker
CAD = coronary artery disease
CCB = calcium-channel blocker
CI = confidence interval
HF = heart failure
RCT = randomized controlled trial

Selection and quality assessment. Three authors (S.B., M.K., F.H.M) independently assessed trial eligibility and quality. The quality of the trials was assessed based on the following: 1) 0 points for mixed studies and 1 point for nonmixed studies—mixed study indicates studies in which patients could be randomized to either a BB or a diuretic in the BB arm, wherein it is difficult to separate the effects of individual therapy; and 2) 1 point if HF was considered a pre-defined end point and 0 points if not.

Data extraction and synthesis. The primary outcome considered for this analysis was new-onset HF as defined by the trials. Secondary outcomes of interest were all-cause mortality, cardiovascular mortality, myocardial infarction (fatal + nonfatal), and stroke (fatal + nonfatal) considered separately. We extracted the inclusion/exclusion criteria, publication year, the sample size, age, first-line antihypertensive agents used, blood pressure before randomization, blood pressure at the end of the study, length of follow-up, and the outcomes of interest for each of the studies listed earlier. Two authors (S.B., S.P.) independently extracted all trial data in duplicate ($\kappa = 0.96$).

Statistical analysis. Statistical analysis was done using standard software (Stata version 9.0, Stata Corp., College Station, Texas) using the METAN program (17). The pooled effect for each grouping of trials was derived from the point estimate for each separate trial weighted by the inverse of the variance ($1/SE^2$). Heterogeneity was assessed visually using funnel plots, Q (chi-square) statistics, and/or the I^2 statistics (18). If trials were homogeneous ($p > 0.05$), a fixed-effect model was used to calculate pooled effect sizes. Otherwise, a random-effect model of DerSimonian and Laird (19) was applied to calculate overall differences. Publication bias was estimated using the weighted regression test of Egger. A subgroup analysis was performed to evaluate the role of BBs in the elderly versus the young. For this analysis, we defined the younger cohort as studies in which the mean age of the population was <60 years and an elderly cohort as studies in which the mean age of the population was ≥60 years. A sensitivity analysis was performed after excluding mixed BB/diuretic trials in which patients could be randomized to either a BB or a diuretic agent in the BB arm of the trial. A pre-specified post hoc