Beta-blockers as Single-Agent Therapy for Hypertension and the Risk of Mortality among Patients with Chronic Obstructive Pulmonary Disease

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PURPOSE: To assess the association between the type of anti-hypertensive medication and all-cause mortality among patients with chronic obstructive pulmonary disease (COPD).

METHODS: The cohort comprised 1966 patients (mean ± SD age, 65.8 ± 10.7 years) enrolled in general internal medicine clinics at seven Veterans Affairs medical centers between December 1996 and October 1999. Patients had a diagnosis of both COPD and hypertension and were receiving single-agent antihypertensive therapy.

RESULTS: Compared with calcium channel blockers, beta-blockers were associated with a decrease in mortality from any cause after adjusting for propensity for having been prescribed a beta-blocker (hazard ratio = 0.57; 95% confidence interval: 0.33 to 0.89). The association was similar when beta-blockers were compared with all other antihypertensive medications, and the decreased risk of mortality was apparent among patients with pre-existing cardiac disease. Restriction of analyses to long-acting calcium channel blockers or to patients who used beta-agonists did not affect the point estimates. Exposure to the remaining classes of antihypertensive agents was not associated with mortality.

CONCLUSION: Beta-blockers may have beneficial effects in patients who have COPD, pre-existing cardiac disease, and hypertension. Beta-blockers may not be contraindicated among patients with COPD. Am J Med. 2004;117:925–931. ©2004 by Elsevier Inc.

Patients with chronic obstructive pulmonary disease (COPD) often have coexisting cardiovascular disease.

In recent pharmacologic efficacy trials (1–4), cardiovascular disease was often the first or second leading cause of death regardless of the severity of COPD. Due to concern over worsening airflow limitation, beta-blockers are less likely to be prescribed in patients with COPD when otherwise indicated (5,6). However, these agents have been demonstrated to reduce mortality and other important cardiovascular disease outcomes among patients with ischemic cardiac disease (7,8). Indeed, beta-blockers may also be beneficial in COPD patients who have sustained a myocardial infarction (5,9), and one meta-analysis reported no changes in physiologic measures of airflow limitation (10). We sought to explore the risk of all-cause mortality associated with beta-blocker use among patients with both COPD and hypertension.

METHODS

Design and Setting

We performed a cohort study using data from the Veterans Affairs (VA)–funded Ambulatory Care Quality Improvement Project (ACQUIP) (11), a randomized trial that tested whether monitoring patients’ self-reported health and providing regular reports to primary care clinicians improved clinical outcomes and patient satisfaction. ACQUIP sought to enroll all patients actively participating in the general internal medicine clinics of seven VA medical centers: Puget Sound Health Care System, Washington; West Los Angeles, California; Birmingham, Alabama; Little Rock, Arkansas; San Francisco, California; Richmond, Virginia; and White River Junction, Vermont.

Data Collection

As part of ACQUIP, baseline assessment of coexisting conditions was performed using a mailed survey. The baseline health inventory inquired about the presence of 24 chronic conditions, including chronic lung disease, ischemic heart disease, and tobacco use. Weekly searches
of the VA computerized medical record system were performed to determine inpatient and outpatient visits. Data on exposures and covariates were determined at study enrollment, defined as the day that a patient’s health inventory was processed (index date). Outpatient pharmacy records were obtained from each site to ascertain the class of antihypertensive medication used.

Study Subjects and Exposure of Interest
This study included patients enrolled in ACQUIP between December 1996 and October 1999. Only subjects who returned the health inventory and had 2 years of follow-up were considered to have complete information and were included in the analysis. In addition, subjects had to fulfill the following criteria: a self-reported or a coded diagnosis (International Classification of Diseases, Ninth Revision [ICD-9]) in the medical record of COPD and hypertension; receipt of prescription(s) in a single antihypertensive medication class in the year before enrollment; and estimated adherence to the antihypertensive medication regimen of 80% or more during the 90 days before the index date. Compliance with antihypertensive medications was estimated based on methods described by Steiner et al (12,13). The medication classes of interest included beta-blockers, angiotensin-converting enzyme inhibitors, thiazide diuretics, alpha-blockers, other antihypertensive agents, and calcium channel blockers. To assess the association between the dose of antihypertensive agent and mortality risk, we stratified individual medications within each antihypertensive class into three dosage levels based on the modal dose. For example, in the 90 days before the index date, the modal daily dose of atenolol was 50 mg. All daily doses of atenolol below 50 mg were considered below the mode, whereas those above 50 mg were considered above the mode. The study was approved by the Human Subjects Committee of the University of Washington.

Outcome
The primary outcome was all-cause mortality during the 2-year follow-up period. Deaths were identified using the VA computerized medical record system and the Beneficiary Identification and Records Locator Subsystem; this combined assessment has been recommended (14) and has been demonstrated to be 98% accurate at identifying deaths (15). A secondary outcome measure was the first hospitalization for exacerbation of COPD during the follow-up period. We defined a COPD hospital admission as a primary ICD-9 discharge diagnosis of COPD (codes 491.x, 492.x, 493.2, 496.x).

Potential Confounding and Effect-Modifying Variables
We adjusted for overall comorbidity using the Seattle Index of Comorbidity (16), which is derived from outpatients’ self-reports and has been demonstrated to predict mortality and resource utilization. We also used several proxy measures of COPD severity. We defined a previous COPD exacerbation within 1 year before the index date as either a primary inpatient discharge diagnosis of COPD (codes 491.x, 492.x, 493.2, 496.x) or an outpatient diagnosis of COPD accompanied by prescriptions for both antibiotics and prednisone within 7 days of the visit. We computed the number of ipratropium bromide canisters and beta-agonists prescribed during the 6 months before the index date. We defined the presence of cardiac disease as either a self-reported diagnosis of prior coronary artery disease, myocardial infarction, angina, history of coronary artery bypass procedure, or chronic heart failure, or a previous medical record diagnosis of atherosclerosis (code 440.x), myocardial ischemia (codes 412.x, 413.x, 414.x, 429.x), acute coronary syndrome (codes 410.x, 411.x), or chronic heart failure (codes 428.x, 398.91, 425.x). We defined atrial fibrillation as an inpatient or outpatient ICD-9 classification diagnosis of 427.3, 427.31, and 427.32.

Statistical Analysis
We used Cox proportional hazards models and stratification to adjust for potential confounding factors and to estimate the relative risk of death. The exposure of interest, the antihypertensive medication class, was entered as an indicator variable. Because calcium channel blockers and beta-blockers have similar indications for cardiovascular disease treatment, we chose calcium channel blockers as the reference group for all analyses. Because of the potential for bias by indication, we also developed propensity scores using logistic regression models. We calculated the probability of being on beta-blockers and stratified the cohort into four quartiles to check for balance between covariates and beta-blockers. As a measure of sensitivity, we also determined if changing the reference group (calcium channel blockers) to all other antihypertensive medications would affect results.

Seattle Index of Comorbidity scores as well as proxy measures of lung disease severity were initially entered individually in bivariate analyses and then entered en bloc into the model. Propensity scores were added, containing antihypertensive medication classes alone, followed by propensity scores, comorbidity scores, and measures of lung disease severity. We assessed potential effect-modifying variables by adding multiplicative interaction terms to the models. All statistical tests were two-tailed, and P values <0.05 were used to define statistical significance. Analyses were performed using SPSS (SPSS Inc, Chicago, Illinois).

RESULTS
We identified 1966 COPD patients with hypertension (2.5% were women) who had also been treated with a
drug from a single antihypertensive medication class. Compared with patients receiving calcium channel blockers (Table 1), those taking beta-blockers were similar with regard to Seattle Index of Comorbidity scores and prevalence of chronic heart failure or diabetes, but were more likely to have cardiac disease ($P = 0.02$) or a previous diagnosis of acute coronary syndrome ($P < 0.001$).

Similar proportions of patients taking beta-blockers and calcium channel blockers had experienced COPD exacerbations during the prior 12 months, although those taking beta-blockers had filled fewer inhaled bronchodilator canisters.

### Association between Antihypertensive Medication Class and Risk of All-Cause Mortality

During the 2-year follow-up, 12.1% of patients died. Compared with patients who filled calcium channel blocker prescriptions, those who received beta-blockers had an approximate 50% reduction in all-cause mortality (Table 2). Adjustment for comorbidity scores and lung disease severity did not significantly change the association between beta-blockers and all-cause mortality. Similarly, adjusting for the propensity for having been prescribed beta-blockers had a small effect on the risk of mortality (hazard ratio [HR] = 0.57; 95% confidence interval [CI]: 0.33 to 0.89). The addition of comorbidity and lung disease severity measures did not significantly change the estimated risk of death over the prior model’s, which contained propensity score alone (HR = 0.59; 95% CI: 0.34 to 1.02).

Eliminating the 46 patients who received short-acting calcium channel blockers (total n = 1920) did not significantly affect mortality risk (unadjusted HR = 0.59; 95% CI: 0.34 to 1.02). Mortality among patients who had filled prescriptions for other classes of antihypertensive agents was similar to those who had received calcium channel blockers. In the analysis in which the reference category was changed from calcium channel blockers to the remaining antihypertensive agents (except beta-blockers), and that adjusted for coexisting illnesses and COPD severity, beta-blockers remained associated with significantly decreased mortality. Compared with all other antihypertensive agents, adjusting for the propensity of being prescribed a beta-blocker had a modest effect on the risk of all-cause mortality (HR = 0.67; 95% CI: 0.39 to 1.14).

### Association between Beta-blocker Dose and Risk of All-Cause Mortality in Patients with a History of Cardiac Disease

Of patients taking beta-blockers, 88% were taking either metoprolol or atenolol with a modal dose of 50 mg/d for
both, and 9% were taking propranolol. Compared with patients taking calcium channel blockers, after adjusting for propensity score, all dosage levels of a beta-blocker were associated with lower mortality (Table 3). When analyses were restricted to patients with a history of prior cardiac disease and adjusted for propensity score, the reduction in mortality associated with beta-blockers appeared to pertain only to patients with pre-existing cardiac disease (Table 4). This association was not affected significantly by changing the reference group from calcium channel blockers to all other antihypertensive agents. Compared with all other antihypertensive agents, calcium channel blockers did not appear to be associated with an elevated mortality risk. Adding an interaction term that contained beta-blockers and cardiac disease history did not improve the model significantly (interaction term $P > 0.20$).

**Beta-blockers, Beta-agonists, and Risk of Death**

To assess if use of beta-agonists attenuated the effects of beta-blockers among patients who had a myocardial infarction, we performed an analysis in which patients were stratified by whether they had received beta-agonist canisters in the previous 6 months and found that beta-agonists did not appear to modify the effects of beta-blockers on all-cause mortality (no beta-agonist: HR $= 0.53; 95\%$ CI: 0.26 to 1.12; received beta-agonist: HR $= 0.67; 95\%$ CI: 0.31 to 1.49). There was also no difference in mortality when patients were stratified by receipt of COPD treatment. Adjusting for the propensity for beta-blockers, the hazard ratio among subjects who received bronchodilators (ipratropium bromide or beta-agonist) was 0.57 ($95\%$ CI: 0.26 to 1.25), compared with 0.58 ($95\%$ CI: 0.31 to 1.06) in those who did not receive bronchodilators.

**Beta-blockers and Risk of COPD Exacerbations**

During the 2-year follow-up, 81 patients had a primary discharge diagnosis of COPD. Compared with patients who had filled prescriptions for calcium channel blockers, patients who had filled prescriptions for beta-blockers had an unadjusted COPD exacerbation risk of 0.46 ($95\%$ CI: 0.21 to 1.04) and, after adjusting for the propensity for beta-blocker use, a risk of 0.65 ($95\%$ CI: 0.29 to 1.48). Adding the number of beta-agonist and ipratropium bromide canisters dispensed, Seattle Index of Co-morbidity (including age), and previous COPD exacerbations to a model that contained propensity for beta-blockers did not improve results (HR for exacerbation $= 0.66; 95\%$ CI: 0.29 to 1.50). Restricting these analyses to patients who had received inhaled bronchodilators in the previous 180 days had little effect on the association between beta-blockers and COPD exacerbation risk (unadjusted HR $= 0.56; 95\%$ CI: 0.22 to 1.44; adjusted HR $= 0.68; 95\%$ CI: 0.26 to 1.76). Restricting the analysis to patients who had previous COPD exacerbations in the
prior year also did not change the results significantly (adjusted HR = 0.56; 95% CI: 0.16 to 1.93).

**DISCUSSION**

We found that among COPD patients with hypertension, beta-blockers were associated with a reduction in all-cause mortality. The risk reduction appeared similar, although not consistently statistically significant, when an alternative reference group of all other antihypertensive agents was chosen. Because of the high prevalence of ischemic heart disease among these patients, we hypothesize that the apparent benefit of beta-blockers may be related to a reduction in adverse cardiovascular events. The observed association was among patients with a previous history of cardiac disease, suggesting a beneficial effect similar to that found among patients without COPD. Perhaps more importantly, we found no evidence of harm associated with beta-blocker use even at higher doses. These findings serve to counter the reticence of many practitioners to prescribe these drugs for COPD patients owing to concerns about worsening their patients’ disease (6).

There was no evidence that patients who took betablockers had less severe lung disease or other medical problems than those who took calcium channel blockers. Although patients who filled prescriptions for beta-blockers obtained fewer bronchodilator canisters, they had similar numbers of previous COPD exacerbations. It is possible that some of the beneficial effects observed reflected residual confounding, after adjustments for disease severity and coexisting conditions were made.

We also found that beta-blockers did not appear to increase the risk of COPD exacerbation. Sensitivity and restriction analyses demonstrated that the effect did not appear to be restricted to either patients who had prior exacerbations or those treated with bronchodilators. Although the point estimate suggested fewer exacerbations, the effect was not statistically significant. Potential biologic and nonbiologic explanations may include the upregulation of beta-receptors and improved bronchodilator responsiveness associated with beta-blocker use (17) or the influence of lung disease severity on beta-blocker prescribing practices (5,6). Nonetheless, because of relatively few events and the potential for residual confounding by severity of pulmonary disease, these results should be interpreted with caution.

Our results are in general agreement with prior studies involving patients with previous myocardial infarction (5,9). Unlike studies involving patients discharged from hospitals, our subjects represented patients with hypertension and COPD in seven general internal medicine clinics. In addition, exposure measures in previous studies were limited to single beta-blocker prescriptions at hospital discharge without refill compliance measures or beta-blocker dosages. In one of these studies (9), the apparent protective effect of beta-blockers was isolated to COPD patients not taking beta-agonists. This finding greatly limits beta-blocker utility to patients with the mildest COPD severity. Our study, however, demonstrated that having filled prescriptions for short-acting beta-agonists 6 months before the index date did not appear to modify the effects of beta-blockers on all-cause mortality, thereby potentially expanding the utility of beta-blockers for COPD patients. In addition, we were able to assess proxy measures of COPD severity.

This study had several strengths. We studied patients from several centers, minimizing the chance that the patterns of diagnosis or treatment by any single physician or group of clinicians exerted undue influence on the results. The cohort was drawn from a complete clinic population, which reduced the likelihood of selection bias. We used a computerized pharmacy database to ascertain antihypertensive exposure in a comparable, unbiased fashion. The VA provides medications free of charge or with minimal copayments.
and about 99% of veterans enrolled in primary clinics obtain all prescription medications from VA pharmacies (12,13).

Despite these strengths, our study also had important limitations. First, exposure was assessed solely by refills recorded in the VA pharmacy database; it is not known whether the subjects actually consumed their pills. However, this type of exposure misclassification would not invalidate our results unless it occurred differentially among the medication classes. Moreover, we required patients to be at least 80% compliant in filling a single antihypertensive medication class. Second, we were unable to confirm the diagnosis of COPD by spirometry. However, agreement between medical chart review and ICD-9 diagnosis for COPD has been reported to be 94.2% (18). Furthermore, we adjusted for important factors associated with COPD morbidity, including smoking status, previous COPD exacerbations, and inhaled bronchodilator use. Third, the study had few women. Finally, we could not adjust for the degree of blood pressure control. We selected patients who were receiving a single antihypertensive medication who would likely have less severe hypertension, and evidence suggests that beta-blockers have similar efficacy to other antihypertensive medication classes (19).

Cardiovascular disease is a leading cause of death among COPD patients (1,2,4), and observational studies suggest that beta-blockers may reduce mortality among COPD patients who have had a myocardial infarction (5,9). Recent meta-analyses have suggested that regular beta-blocker use does not result in decreased forced expiratory flow in patients with obstructive lung disease, but rather leads to improved bronchodilator response (10,17). Our study suggests that compared with calcium channel blockers and other antihypertensive agents, beta-blockers were associated with decreased risk of all-cause mortality among patients with COPD. Although no interaction was detected between cardiac disease and beta-blocker use for mortality risk, we observed a significant reduction in the risk of death associated with beta-blocker use among patients with cardiac disease. We cannot conclude that beta-blockers reduce mortality among patients with COPD; however, the results strongly suggest that beta-blockers are safe as they are currently being prescribed. Randomized studies are needed to evaluate the safety and efficacy of beta-blockers among these patients.

**REFERENCES**


2. Burge PS, Calverley PM, Jones PW, et al. Randomised, double-blind, placebo controlled study of fluticasone propionate in pa-

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**Table 4. Association of Antihypertensive Agents and Risk of Mortality among Patients with Chronic Obstructive Pulmonary Disease and Hypertension, Stratified by History of Cardiac Disease and Chronic Heart Failure**

<table>
<thead>
<tr>
<th>Antihypertensive Medication</th>
<th>Alive (n = 1273)</th>
<th>Dead (n = 228)</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
<th>Adjusted for Seattle Index of Comorbidity and proportionate bronchodilator use before the index date.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium-channel blocker</td>
<td>11</td>
<td></td>
<td>0.41 (0.22–0.78)</td>
<td>Adjusted for Seattle Index of Comorbidity with age, history of exacerbation of chronic obstructive pulmonary disease, and number of beta-agonist and ipratropium bromide canisters filled in the 6 months before the index date.</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>171</td>
<td>11</td>
<td>0.68 (0.46–1.01)</td>
<td>Adjusted for Seattle Index of Comorbidity and proportionate bronchodilator use before the index date.</td>
</tr>
<tr>
<td>All other antihypertensive agents</td>
<td>434</td>
<td>88</td>
<td>0.71 (0.44–1.14)</td>
<td>Adjusted for Seattle Index of Comorbidity and proportionate bronchodilator use before the index date.</td>
</tr>
</tbody>
</table>

- Model 1: Compares all agents with calcium channel blockers (referent).
- Model 2: Compares beta-blockers and calcium channel blockers with a pooled referent group consisting of all other antihypertensive agents.
- Adjusted for Seattle Index of Comorbidity and proportionate bronchodilator use before the index date.


