Beta-blocker use and the risk of death in hospitalized patients with acute exacerbations of COPD

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ABSTRACT

Background: Cardiovascular disease is a major cause of death among COPD patients and predicts hospitalization for acute exacerbation, in-hospital death, and post-discharge mortality. Although beta-blockers improve cardiovascular outcomes, COPD patients often do not receive them due to concerns about possible adverse pulmonary effects. There are no published data about beta-blocker use among inpatients with COPD exacerbations. We aimed to identify factors associated with beta-blocker use in this setting and to determine whether their use is associated with decreased in-hospital mortality.

Methods: We reviewed administrative data from the University of Alabama Hospital and identified patients admitted between October 1999 and September 2006 with acute exacerbation of COPD as primary diagnosis or as secondary diagnosis with a primary diagnosis of acute respiratory failure. Demographics, co-morbidities, and medication use were recorded and subjects receiving beta-blockers were compared to those who did not. Multivariate regression analysis was performed to determine predictors of in-hospital death after controlling for known covariates and the propensity to receive beta-blockers.

Results: 825 patients met inclusion criteria. In-hospital mortality was 5.2%. Those receiving beta-blockers (n=142) were older and more frequently had cardiovascular disease than those who did not. In multivariate analysis adjusting for potential confounders including the propensity score, beta-blocker use was associated with reduced mortality (OR=0.39; 95% CI: 0.14-0.99). Age, length of stay, number of prior exacerbations, the presence of respiratory failure, congestive heart failure, cerebrovascular disease, or liver disease also predicted in-hospital mortality (p<0.05).

Conclusions: Beta-blocker use among inpatients with exacerbations of COPD is well tolerated and may be associated with reduced mortality. The potential protective effect of beta-blockers in this population warrants further study.
INTRODUCTION
COPD is the fourth leading cause of death in the United States and the only major cause that is rising in frequency [1]. Although many patients with COPD die from respiratory failure, cardiovascular disease is consistently the 1st or 2nd leading cause of death depending on the severity of the participants’ underlying lung disease and the individual study population [2-6]. Most of these cardiovascular deaths are due to coronary artery disease which is present in 10% to 22% of COPD patients [7, 8]. This can be attributed to their high prevalence of traditional cardiovascular risk factors (e.g. tobacco use, hypertension, etc.) and those more recently reported such as systemic inflammation and medication toxicity [7-12]. Many COPD deaths occur during hospitalization for acute exacerbations, a complication which carries an in-hospital mortality as high as 32% and predicts a one year mortality of 23-43% [13-18]. Although these deaths are often attributed to underlying COPD, the contribution of cardiac disease is thought to be significant [15-17].

Beta-blockers reduce mortality in patients with cardiovascular disease, most notably after myocardial infarction [19], in the presence of congestive heart failure [20], and in the perioperative setting [21]. Patients with COPD are often denied these medications because of possible adverse effects of beta-blockade on airway function [19, 22]. This practice continues despite the fact that studies with cardioselective beta-blockers have shown the airway effect to be modest at most [23]. A recent Cochrane Review analyzing 20 randomized trials of cardioselective beta-blockers in COPD found no significant effect on FEV1 or bronchodilator response after single doses or up to 12 weeks of treatment [23]. This was true even among patients with severe COPD and those with reversible airflow obstruction. Moreover, beta-blockers have been shown to reduce mortality in COPD patients with hypertension as compared to other agents [24] and to blunt the apparent cardiac toxicity of short acting beta-agonists [12]. Although there has been more concern about the airway effects of non-cardioselective beta-blockers [25] there is data that they are well tolerated in patients with COPD and congestive heart failure [26].

Despite the apparent safety and potential benefit of beta-blocker use in COPD patients with all levels of disease severity, little is known about their effects during inpatient admissions for acute exacerbations where airway function is most severely compromised. The purpose of this study was to examine the use of beta-blockers (both cardioselective and non-cardioselective) in patients admitted to a university hospital with acute exacerbations of COPD and to determine whether the administration of these drugs was associated with in-hospital mortality. We found that beta-blocker use was an independent predictor of survival to hospital discharge.
METHODS

The study was approved by the University of Alabama at Birmingham Institutional Review Board. We reviewed the computerized hospital record system and identified patients admitted to our facility between October 1, 1999 and September 30, 2006 whose discharge or death summaries indicated a primary diagnosis of acute exacerbation of COPD (International Classification of Diseases, Ninth Edition (ICD-9) code 491.21) or a primary diagnosis of acute respiratory failure (518.81) and a secondary diagnosis of acute exacerbation. Patients with a diagnosis of asthma (493) were excluded. Demographic data including age, race, and sex; date of index admission (defined as the final admission during the study period); number of prior admissions for acute exacerbation of COPD during the study period; smoking status; attending physician of record and medical subspecialty service were recorded at the time of hospital admission. The presence of respiratory failure and co-morbid illness including cardiovascular disease, diabetes mellitus, liver disease, chronic renal insufficiency, and malignancy were determined by ICD-9 coding and the total disease burden was assessed using the Deyo-Charlson index [27]. Lengths of stay and hospital disposition were also recorded. Inpatient medication use was determined by automated billing records. Patients were considered to have received a given agent if he or she was billed for any formulation of the drug at any time during the hospitalization. For each drug, the number of doses per hospital day was also calculated. Beta-blockers were categorized as cardioselective or non-cardioselective. We also reviewed records from our health system’s pulmonary function laboratory and recorded a patient’s spirometric data if it was present and obtained within one year of the index admission.

Demographics, diagnostic profile, medication use, and in-hospital mortality were compared between subjects who received beta-blockers and those who did not. Continuous variables were compared using Student’s t-tests and categorical variables were compared using the chi square or Fisher exact test as appropriate.

A propensity score technique was used as an additional method to balance covariates associated with beta-blocker use between groups [28]. The propensity score was recorded as a continuous variable and was derived from a logistic regression model with beta-blocker use as a dichotomous dependent variable. We included all recorded demographic factors, co-morbid illnesses, and treatments as potential covariates in the propensity score model. Variables were entered and maintained in the model if they had a p-value <0.20 in the final model.

A multivariate logistic regression model including all patient characteristics as well as the propensity score was then optimized using backward selection and analyzed to identify predictors of in-hospital mortality. Interaction terms between beta-blocker use and each of the variables in the database were also included. Variables were omitted from the model if they were not significant and their removal altered the estimate of beta-blocker effect by less than 10 percent. Additional models were developed to examine the relationship between the average number of daily doses of beta-blockers and short-acting beta agonists and mortality. In an effort to address the possibility of confounding by indication, we also compared the point estimate for the effect of beta-blockers to that of calcium channel blockers in mutually exclusive subgroups. Calculations were performed using SPSS, Version 15.0 statistical software and p-values < 0.05 were considered significant.
RESULTS

A total of 825 patients admitted to University Hospital between October 1, 1999 and September 30, 2006 met inclusion criteria. Table 1 reports the univariate comparison of characteristics divided by beta-blocker use.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Beta-blockers Mean +/- SD or Number (%)</th>
<th>No Beta-blockers Mean +/- SD or Number (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>68 +/- 11</td>
<td>65 +/- 13</td>
<td>0.01</td>
</tr>
<tr>
<td>Female</td>
<td>71 (50)</td>
<td>344 (50)</td>
<td>1</td>
</tr>
<tr>
<td>Caucasian race</td>
<td>82 (58)</td>
<td>429 (63)</td>
<td>0.30</td>
</tr>
<tr>
<td>Number of prior admissions for AECOPD</td>
<td>1.4 +/- 1.1</td>
<td>1.6 +/- 1.6</td>
<td>0.10</td>
</tr>
<tr>
<td>Mean length of stay, days</td>
<td>7.8 +/- 12.9</td>
<td>5.3 +/- 7.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Deyo-Charlson Index</td>
<td>2.4 +/- 1.3</td>
<td>1.9 +/- 1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Co-morbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>87 (61)</td>
<td>219 (32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>22 (15)</td>
<td>48 (7)</td>
<td>0.002</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>71 (50)</td>
<td>157 (23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>11 (8)</td>
<td>36 (5)</td>
<td>0.34</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>12 (8)</td>
<td>22 (3)</td>
<td>0.01</td>
</tr>
<tr>
<td>Malignancy</td>
<td>5 (4)</td>
<td>35 (5)</td>
<td>0.55</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>36 (25)</td>
<td>126 (18)</td>
<td>0.08</td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>10 (7)</td>
<td>52 (8)</td>
<td>0.86</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>2 (1)</td>
<td>11 (2)</td>
<td>1</td>
</tr>
<tr>
<td>Current smoking</td>
<td>78 (55)</td>
<td>363 (53)</td>
<td>0.76</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>24 (17)</td>
<td>85 (12)</td>
<td>0.20</td>
</tr>
<tr>
<td>Admitted to pulmonary specialist service</td>
<td>82 (58)</td>
<td>404 (59)</td>
<td>0.82</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>8 (6)</td>
<td>35 (5)</td>
<td>0.83</td>
</tr>
</tbody>
</table>

Patients in both groups were predominantly Caucasians and there were a similar number of men and women. A majority of patients were admitted to a pulmonary subspecialty ward. Patients treated with beta-blockers were older, had longer hospital stays, and were more likely to have cardiovascular disease and greater total co-morbidity as measured by the Deyo-Charlson score. There was no difference in the frequency of respiratory failure or in-hospital mortality between the two groups.

Table 2 compares concomitant medication use in the two groups.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Beta-blockers Number (%)</th>
<th>No Beta-blockers Number (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic steroid</td>
<td>130 (92)</td>
<td>634 (93)</td>
<td>0.73</td>
</tr>
<tr>
<td>Inhaled steroid</td>
<td>7 (5)</td>
<td>51 (7)</td>
<td>0.37</td>
</tr>
<tr>
<td>Antibiotic</td>
<td>128 (90)</td>
<td>585 (86)</td>
<td>0.20</td>
</tr>
<tr>
<td>Short acting beta-agonist</td>
<td>133 (94)</td>
<td>657 (96)</td>
<td>0.26</td>
</tr>
<tr>
<td>Long acting beta-agonist</td>
<td>8 (6)</td>
<td>37 (5)</td>
<td>0.92</td>
</tr>
</tbody>
</table>
Patients who did not receive beta-blockers were more likely to be treated with methlyxanthines (theophylline or aminophylline) but other medication use was similar between the two groups. Cardioselective beta-blockers were administered to 121 patients (metoprolol and atenolol were most common) while 24 patients received non-cardioselective agents (carvedilol in 17).

In comparison to patients who survived, those who died were older (71 vs. 65 years, p<0.001), had longer hospital stays (17 vs. 5 days, p<0.001), and were more often cared for on the pulmonary service (79% vs. 58%, p=0.006). Those who died also had more prior exacerbations (2.7 vs. 1.5, p<0.001) and were more likely to have cardiovascular disease (67% vs. 35%, p<0.001), respiratory failure (58% vs. 11%, p<0.001), and higher Deyo-Charlson scores (2.5 vs. 2.0, p=0.013). Among those who died, care was withdrawn in 8 and an additional 26 had “do not resuscitate” orders prior to their deaths. While all 43 were admitted for acute exacerbations of COPD, the most frequent complications leading to death were nosocomial infection or progressive multiorgan failure (n=12), myocardial infarction (n=4), and renal failure (n=4).

Predictors of in-hospital mortality are shown in Table 3.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unadjusted OR for Death (95% CI)</th>
<th>P Value</th>
<th>Adjusted OR for Death (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blocker use</td>
<td>1.10 (0.50-2.44)</td>
<td>0.80</td>
<td>0.39 (0.14-0.99)</td>
<td>0.049</td>
</tr>
<tr>
<td>Short-acting beta-agonist use</td>
<td>0.08 (0.04-0.17)</td>
<td>&lt;0.001</td>
<td>0.08 (0.02-0.30)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, per year of life</td>
<td>1.05 (1.02-1.08)</td>
<td>0.001</td>
<td>1.05 (1.02-1.09)</td>
<td>0.004</td>
</tr>
<tr>
<td>Number of prior AECOPD</td>
<td>1.27 (1.12-1.44)</td>
<td>&lt;0.001</td>
<td>1.22 (1.01-1.47)</td>
<td>0.037</td>
</tr>
<tr>
<td>Length of stay, per day</td>
<td>1.06 (1.04-1.09)</td>
<td>&lt;0.001</td>
<td>1.05 (1.02-1.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>11.5 (6.04-22.0)</td>
<td>&lt;0.001</td>
<td>10.2 (4.58-22.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>3.58 (1.92-6.67)</td>
<td>&lt;0.001</td>
<td>4.54 (1.53-13.5)</td>
<td>0.006</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>3.41 (1.25-9.32)</td>
<td>0.016</td>
<td>12.9 (3.10-53.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>3.42 (0.73-15.9)</td>
<td>0.12</td>
<td>12.1 (2.06-71.5)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

The original model included all factors listed in Tables 1 and 2 as well as the propensity score and interaction terms between the use of beta-blockers and each of the other variables. No significant interactions were found. The R² of the final adjusted model shown in Table 3 was 0.38. Age, increasing length of stay, respiratory failure, and the number of prior acute exacerbations were associated with an increased risk of in-hospital death. The presence of congestive heart failure, cerebrovascular disease, and liver disease also predicted increased mortality. The use of beta-blockers (OR = 0.39; 95% CI: 0.14-0.99) and short-acting beta-agonists (OR = 0.08; 95% CI: 0.02-0.30) were associated with reduced mortality. We also found a significant association between the number of daily doses of beta-blocker and mortality (OR = 0.31; 95% CI: 0.12-0.80) though no dose response relationship was observed with short-acting beta-agonists (OR = 1.02; 95% CI: 0.70-1.47). The point estimates for the effect of beta-blockers were similar when stratified for the presence or absence of cardiovascular disease (OR = 0.37 vs. 0.38).
though neither reached statistical significance. The point estimate of the effect of beta-blockers among those who did not receive calcium channel blockers (N=577) was comparable to that of the overall population (OR = 0.34; 95% CI: 0.06-1.81) though not statistically significant (p=0.20). No association between calcium channel blocker use and mortality in those who did not receive beta-blockers was seen (N=683) (OR = 0.76; 95% CI: 0.28-2.06, p=0.60) indicating specificity of the beta-blocker effect.

In the subset of patients with available spirometric data there was no significant difference between those who received beta-blockers and those who did not in percent predicted FEV1 (41% +/- 16% vs. 40% +/-15% predicted, n=44 vs. 240, p=0.67) or FEV1/FVC ratio (0.50 +/- 0.10 vs. 0.53 +/- 0.08, p=0.61).
DISCUSSION

This study examining a large population of inpatients admitted for acute exacerbations of COPD found that beta-blocker use was associated with reduced in-hospital mortality. When evaluated in a multivariate regression model including a propensity score, beta-blocker use was a powerful predictor of outcome. The benefit of beta-blockers was observed despite the fact that those who received the drugs were older, had longer hospital stays, and had a greater prevalence of congestive heart failure and cerebrovascular disease, all factors that were independent predictors of in-hospital mortality. We found no association between calcium channel blocker use and hospital mortality suggesting our results are not due to healthy user bias and that beta-blockers may offer a class specific benefit.

Beta-blockers are often withheld from COPD patients due to the perception that their use is relatively contraindicated [19, 22]. This is despite the fact that cardioselective beta-blockers have no demonstrable effect on lung function regardless of disease severity or bronchodilator reversibility [23] and that COPD patients with cardiac disease appear to derive the same benefits from these drugs as does the general population [19]. Current American Heart Association guidelines for secondary prevention of coronary disease include beta-blockers as a class IA intervention in patients with prior myocardial infarction, acute coronary syndrome, or congestive heart failure [29] and the Centers for Medicaid and Medicare include beta-blocker use following myocardial infarction as a hospital performance measure [30]. In our study, only 31% (93/298) of patients with COPD and congestive heart failure or myocardial infarction received beta-blockers. This is comparable to prior reports [19, 22, 31] that have also suggested that most COPD patients with cardiovascular disease are denied the protective effect offered by these agents.

No prospective studies have specifically examined the effect of beta-blockers on mortality in a large cohort of COPD patients; however, significant observational data support the safety and effectiveness of the drugs when used in this population. Gottlieb reviewed the medical records of all Medicare patients discharged after acute myocardial infarction over an 18-month period and evaluated survival with social security records [19]. After adjustment for covariates, COPD patients who received beta-blockers had a 40% reduction in mortality which was similar to the reduction seen in the entire population. Au examined the association between beta-blocker use and all-cause mortality at two years in a veteran population with COPD and hypertension [24]. As compared to calcium channel blockers, beta-blockers were associated with a reduced risk of death (hazard ratio (HR) = 0.57). When compared to all other antihypertensive agents the results were similar. Importantly, the benefit of beta-blockers was limited to those with cardiac disease (absolute risk reduction 12.8%, p<0.001) and not observed in those without (absolute risk reduction 4.0%, p=0.37) though the study may have been underpowered to detect this small difference. It is also notable that there was actually a trend towards reduced COPD-related hospitalizations among those taking beta-blockers (HR=0.46; CI: 0.21-1.04). Despite the limitations of their retrospective design, these studies suggest a mortality benefit with the use of beta-blockers in patients with COPD who have had a recent myocardial infarction or have other cardiac disease.

Other data indicate that beta-blockers may improve outcomes in COPD patients without known cardiac disease. Mancini showed that COPD patients who suffered a myocardial infarction, were hospitalized for COPD, or died were less likely to be taking beta-blockers regardless of their risk for cardiovascular events [32]. Furthermore, Au
showed that beta-blockers reduced the risk of cardiovascular events even after adjusting for the presence of cardiovascular disease and other risk factors such as smoking, hypertension, and diabetes mellitus [12].

Previous studies have implicated cardiovascular disease as an independent risk factor for hospitalization for COPD [33], in-hospital mortality [15, 16], and mortality after discharge [7, 17]. In an analysis of 1829 Veterans participating in a randomized trial comparing tiotropium to placebo, Niewoehner has found that any cardiovascular disease was an independent risk factor for hospitalization for acute exacerbation (OR=2.10; CI 1.28-3.46, p=0.004) [33]. Ai-Ping also reported that non-survivors of an intensive care unit admission for acute exacerbations were more likely than survivors to have cardiac disease (85% vs. 37%, p=0.002) [16]. Similarly, in a multivariate analysis of factors associated with in-hospital death during acute exacerbations, Fuso found that variables reflecting cardiovascular dysfunction were among the key determinants of risk [15].

In addition to the apparent protective effect of beta-blockers, we found that treatment with short acting beta-agonists was associated with reduced mortality. This finding is unexpected based on prior reports suggesting that these agents may increase the risk of cardiovascular morbidity when used chronically in the outpatient setting [10-12]. It is possible that this result reflects the avoidance of short acting beta-agonists among patients with the highest risk of death, such as those with tachyarrhythmias or other unstable cardiac disease, rather than a true beneficial effect among recipients. Indeed, although all 43 patients who died were treated with short-acting anticholinergics, 12 were not prescribed short acting beta-agonists suggesting practitioners may have judged them to be unsafe. Of note, the benefit of short-acting beta-agonists was lost when the number of daily doses was examined as the independent variable. When combined with the analysis suggesting a dose-response benefit to beta-blocker use, these results suggest that beta stimulation, whether endogenous or exogenous, may be deleterious for patients with acute exacerbations of COPD. Despite this hypothesis, it remains possible that beta-agonists are beneficial for inpatients with severe exacerbations as they are known to rapidly improve lung function and symptoms in that setting [34]. We found no evidence that beta-blockers reduce the beneficial effects of short-acting beta-agonists when the two are used concomitantly during acute exacerbations. It has been suggested that beta-blockers may in fact improve bronchodilator responsiveness by leading to upregulation of beta receptors within the lung [35] though this requires further study.

Although the use of beta-blockers was an independent predictor of survival in multivariate analysis, univariate analysis did not demonstrate a statistically significant mortality advantage to their use. This underscores the importance of adjusting for the covariates in the model particularly given the greater co-morbidity found in beta-blocker users.

As a retrospective study, this report has important limitations. Although the multivariate analysis can correct for known covariates, limitations in the database may confound the results. For example, it is possible that patients who received beta-blockers had less severe baseline COPD or less serious exacerbations than those who did not. However, the lack of difference between the two groups in the number of prior admissions for acute exacerbations or frequency of respiratory failure suggests this was not the case. The available pulmonary function data also suggest that the severity of airflow obstruction was similar between the two groups. Although other investigators have used pharmacy billing records to measure inpatient medication use [36, 37], Ward
has shown that point of care clinical information systems may capture inpatient medication use more accurately than pharmacy records as they are more closely connected to nursing and respiratory care [38]. This may be particularly true for bronchodilators as they are often administered by staff on an as needed basis. The use of inpatient billing records also prevented the evaluation of outpatient medication use, dosage or adherence and it is not known whether beta-blockers were started in the hospital or continued based on outpatient prescriptions. There may be differences in the effects of chronic beta-blocker use and the new administration of these drugs during acute exacerbations and this warrants further investigation. The acute withdrawal of beta-blockers has been associated with an increased risk of myocardial infarction [39] and it is possible that our results could be partly explained by adverse effects of this practice among patients whose beta-blockers were discontinued on admission. Lastly, larger studies are needed to better define whether the mortality benefit of beta-blockers in this setting is observed with cardioselective agents, non-cardioselective agents, or both.

In summary, the results of this study suggest that the use of beta-blockers in patients admitted with acute exacerbations of COPD is not deleterious and may be associated with a beneficial effect on mortality. These results have direct implications for the use of beta-blockers in patients hospitalized for acute exacerbations of COPD and suggest that they can be safely continued in this setting. The strength of these and other observational data supporting the safety and potential efficacy of beta-blockers in patients with COPD now support the pursuit of randomized trials in the outpatient setting. If our results are confirmed, prospective trials among inpatients with acute exacerbations should also be considered.
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