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Beta-blockers for the treatment of cardiovascular disease in COPD patients

By

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Introduction

Patients with chronic obstructive pulmonary disease (COPD) have high rates of cardiovascular comorbidities, including hypertension, ischemic heart disease, and heart failure.¹ These comorbidities further complicate management of COPD patients. Cardiovascular complications are especially difficult to manage during acute exacerbations of chronic obstructive pulmonary disease (AECOPD). Multiple factors are contributory, including hypoxemia, tachycardia, increased inflammation, and arterial stiffness.² Cardioselective beta-blockers have been proven to be safe and effective in managing cardiovascular conditions such as heart failure and arrhythmias and are recommended for acutely decompensated heart failure and myocardial infarction in the setting of AECOPD. Benefits include reducing all-cause mortality and the risk of COPD exacerbations.¹ However, beta-blockers continue to be underused in COPD patients due to lingering concerns about bronchospasm leading to exacerbation of COPD symptoms requiring hospitalization.³ Whether the use of beta-blockers for cardiovascular disease in patients with COPD would decrease pulmonary function or increase frequency of exacerbations, hospitalizations, and mortality will be examined.

Discussion

Findings

In retrospective and observational studies, the use of cardioselective beta-blockers decreases mortality and increases survival rates, especially in the acute setting. In a study by Wang et al. done in Taiwan, patients with newly diagnosed acute myocardial infarction (AMI) and concurrent COPD (23,116 participants), the treatment of the AMI was categorized as beta-blockers, both selective (2,859) and non-selective (4,750), and those treated without beta-

blockers (15,507). Patients treated with beta-blockers had a higher prevalence of co-morbidities such as hypertension, diabetes, and end-stage renal disease. Patients with cardio-selective beta-blockers were also more like to be treated with percutaneous coronary intervention (PCI), indicating more severe cardiovascular disease. However, patients treated initially with cardioselective beta-blockers had a statistically significant reduced mortality risk (HR 0.93) and increased both short-term and long-term survival rates compared with patients not treated with beta-blockers.⁴ In the acute setting, the benefits seemed to outweigh the risks for treating COPD patients with cardioselective beta-blockers during an AMI. Although mortality was decreased, this study did not look at the long-term morbidity or adverse effects from the use of beta-blockers after discharge from the hospital. Due to the limited amount of information from coding data from insurance companies, there was no way to track if beta-blockers were continued as long-term treatment for the patient. Similarly, in Austrian patients with COPD who were treated for coronary artery disease (CAD) with beta-blockers in 2006 (n=12,628), Rezaei et al. found that 6.9% of patients treated with beta-blockers died in the initial 6 month treatment period, compared with 22.6% of 3,647 patients not treated with beta-blockers died in the initial 6 month treatment period in 2006 and 9.6% of 14,041 beta-blocker users and 21.4% of 4,607 non-users died in 2007.⁵ Although this study had a large population size, the use of ICD-10 codes provided limited information on the severity of COPD and the adherence of the beta-blockers once the prescription was filled.

However, this benefit was mostly seen with cardioselective beta-blockers. In an Italian population-based cohort study by Sessa et al., 51,124 COPD patients in total were treated for heart failure, with 39,370 (76.9%) treated with cardioselective beta-blockers metoprolol, bisoprolol, and nebivolol and 11,844 (23.1%) with the non-cardioselective beta-blocker

carvedilol. Patients treated with carvedilol had a higher risk for heart failure hospitalization (HR 1.29, CI 1.18-1.40, $p < 0.001$), accounted for 26.8% of heart failure hospitalizations (95%CI 22.5-30.9%; p -value < 0.001), and were more likely to discontinue carvedilol due to complications with 131 additional cases of beta-blocker discontinuation per 10,000 person-years compared to patients using cardio-selective beta-blockers ($p < 0.001$).⁶ The study had a long follow-up period of five years but relying on local health administration databases for information regarding hospitalization made it possible some patients could have been hospitalized outside the system and thus, not included in the data. The diagnoses for the beta-blocker prescriptions were not specified, allowing for asthma patients (who are known to have more adverse effects to beta-blockers than COPD patients) to be included in the data.

The evidence from this study was corroborated by Huang et al. in their population-based nested case control study of 16,067 case participants and 55,970 control participants. Patients treated with noncardioselective beta-blockers such as labetalol and propranolol had an increased risk of severe exacerbations (OR 1.49, CI 1.32-1.67 for labetalol, OR 1.16, 95% CI 1.10 – 1.23 for propranolol) compared with patients treated with selective beta-blockers such as betaxolol (OR 0.75, 95% CI, 0.60 -.95).⁷ Furthermore, betaxolol had the lowest adjusted odds ratio (0.75) compared with cardioselective beta-blockers metoprolol (0.88), bisoprolol (0.85), and atenolol (0.97).⁷ Researchers were able to use generalized additive models (GAMs) to model the duration and amount of beta-blockers patients were taking to accurately correlate the dosage of beta-blockers with AECOPD.⁷ However, pulmonary function testing or quality of life questionnaires were not examined to assess the severity of COPD.

In addition to evidence beta-blockers are the safer choice for the treatment of both AMI and HF in COPD patients, beta-blockers were also found to be superior to non-dihydropyridine

calcium channel blockers (NDCCB) in the treatment of AMI, which are often used as alternatives to beta-blockers. When both were compared, patients treated with beta-blockers had statistically significant overall lower mortality (HR 0.91, CI 0.83-0.99) compared with those treated with NDCCB (HR 0.91, CI 0.83-0.99).⁸ Beta-blockers also decreased re-admissions due to COPD exacerbations by 12-32% and these patients were less likely to use acute medical services in one year for obstructive lung disease (HR 0.74, CI 0.69-0.80), which was statistically significant.⁸ Although the study was limited as an observational study using data from an insurance claims database, it is one of the first studies to compare beta-blockers with NDCCBs. In a similar but smaller study by Zvizdic et al. 68 patients with moderate COPD, defined as Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage II, and severe COPD (GOLD stage III), were treated with a combination of verapamil, a NDCCB, and digoxin or a cardioselective beta-blocker. In patients with moderate and severe COPD, no statistically significant differences were found in the number of acute exacerbations between the patients treated with verapamil and digoxin versus cardioselective beta-blockers.⁹ In fact, patients in the beta-blocker group had a decrease in the number of exacerbations in patients with moderate COPD (0.600 compared with 1.333, $p < 0.007$).⁹ This study not only compared cardioselective beta-blockers with NDCCB but also examined the beta-blockers with varying degrees of COPD.

The principal concern for many providers prescribing beta-blockers is the potential negative effect these drugs may have on pulmonary function in COPD patients. However, evidence from many studies has indicated reduced pulmonary function is not associated with beta-blocker use, especially cardioselective beta-blockers. In their cohort study of 5,162 patients, 557 of whom received beta-blockers, Maltais et al. used data from the multinational, multicenter, randomized, double-blind TONADO study showing similar lung function, measured

by FEV₁, in moderate to severe patients treated with and without beta-blockers with a difference of 0.010L (95% CI -0.009 – 0.028) in the FEV₁ between the two groups. The patients were also being treated with long-acting bronchodilators tiotropium and olodaterol. The quality of life measured by St. George's Respiratory Questionnaire (SGRQ) showed no statistically significant difference between COPD patients being treated with beta-blockers compared with those who were not being treated with beta-blockers.¹⁰ The concurrent use of long-acting bronchodilators and beta-blockers was unique to this study and further quells fears providers have of interactions between the two. Jabbal et al. also found in a small, randomized, open label cross-over study of eighteen former smokers that patients treated specifically with bisoprolol, a cardioselective beta-blocker, had a statistically significant higher FEV₁s and lung compliance, measured by area under the reactance curve (AX), compared with carvedilol with no statistically significant changes in these factors seen from baseline for the bisoprolol group.¹¹ This difference was especially true in patients treated with a long-acting beta2 agonist (LABA) and an inhaled corticosteroids (ICS), further showing no interaction between LABAs and cardioselective beta-blockers.¹¹ Although this trial was one of the few randomized studies performed, the small sample size should be noted. Many of the authors also receive personal fees from pharmaceutical companies such as Pfizer, AstraZeneca, and Boehringer Ingelheim. Dransfield et al. also showed treatment of COPD patients with beta-blockers did not interfere with COPD treatment regimens, including therapies with LABAs or ICSs. Using 5,159 participants with baseline beta-blocker therapy from the Study to Understand Mortality and Morbidity in COPD (SUMMIT), no statistically significant differences in FEV₁ were seen at three, six, nine, or twelve months; no increases in COPD exacerbations or increased risks of cardiovascular events

were found.¹² It is also important to note this study was also funded by the pharmaceutical company GlaxoSmithKline.

In addition to the lack of harmful effects on COPD in patients with heart disease, cardioselective beta-blockers may even reduce the amount and severity of COPD exacerbations. In a prospective, multicenter observational cohort study, 3,464 participants of GOLD stage 2 through 4, former and current smokers, use of beta-blockers was associated with a statistically significant reduction of total (IRR 0.73, 95% CI 0.60- 0.90) and severe exacerbations (IRR 0.67, 95% CI 0.49-0.93) with no increase in all-cause mortality.¹³ After adjusting for cardiovascular disease such as CAD and CHF, patients using beta-blockers still had a decrease in total and severe exacerbations and showed no change in the quality of life based on the SGRQ questionnaire.¹³ Even in patients with severe COPD, beta-blocker use was associated with a reduction in total (IRR 0.33, CI 0.19-0.58, $P < 0.001$) and severe COPD exacerbations (IRR 0.35, 95% CI 0.16 – 0.76, $p < 0.05$).¹³

Strengths/Limitations

Most studies had large sample sizes with diverse sampling from countries such as Taiwan, Austria, and others across Europe. Patients also had short-term and long-term follow up, which helped determine both the short-term and long-term consequences of treatment. The studies available looked at the relationship of beta-blockers with COPD patients from various angles, including the number of exacerbations and hospitalization for such exacerbations, mortality, effects on pulmonary function, interactions with COPD therapies, and beta-blockers compared to alternative pharmacotherapies. Some limitations included the retrospective and observational nature of the studies, which cannot provide the same strength of evidence as

prospective trials with randomization of a large and diverse sample of well-matched participants. Many studies often did not specify if patients were treated with a cardioselective or a nonselective beta-blocker, which is an important differentiation. Another limitation was the source of data for many of these studies, which was indirect information collected from insurance or billing agencies in the form of ICD codes, diagnostic tests ordered, and prescriptions ordered and filled. Without direct patient data, errors may occur, such as generally incorrect diagnoses or basing diagnoses or severity of COPD on prescriptions of inhalers, which can be used both for COPD and asthma.

Randomized control studies targeting COPD patients with cardiovascular conditions such as heart failure, arrhythmias, and myocardial infarctions need to be performed to strengthen the currently available evidence. New research should examine endpoints of pulmonary function tests, rate of exacerbations, and the long-term effects of beta-blockers on lung functioning. Study design should specify whether beta-blockers were cardioselective or nonselective. Information derived from further research would enhance clinicians' ability to more effectively manage their COPD patients with cardiovascular disease.

Conclusion

COPD is currently the fourth leading cause of death in the world and is slated to become the 3rd leading cause of death in 2020.¹⁴ Cardiovascular disease is a common comorbidity in COPD patients with mortality being higher from cardiac disease than respiratory disease in patients with moderate COPD.¹⁴ Although clinicians are often hesitant to treat cardiovascular disease with beta-blockers in COPD patients for fear of worsening pulmonary functioning and exacerbating COPD, the evidence suggests otherwise. Beta-blockers, especially cardioselective

beta-blockers have been shown to decrease mortality and increase survival rates especially when treating myocardial infarctions and acute decompensating heart failure.⁴⁻⁷ These treatments do not worsen pulmonary function and do not interact with other treatments for COPD, including long-acting beta agonists.¹⁰⁻¹³ Beta-blockers have also been shown to produce superior outcomes in treatment of cardiovascular disease in COPD patients compared with alternative therapies such as non-dihydropyridine calcium channel blockers.^{8,9} The beneficial pharmacodynamic effects of cardioselective beta-blockers are due to multiple changes in hemodynamics including decreased oxygen demand, reduced sympathetic tone, modulation of chronic inflammation, and increased production of nitric oxide in vascular smooth muscle reducing afterload. These changes are thought to counteract the COPD burden, including arterial stiffness and systemic inflammation, on the cardiovascular system.⁸

Overall, cardio-selective beta-blockers can be used cautiously in COPD patients to treat cardiovascular disease, such as myocardial infarction, heart failure, arrhythmias, and coronary artery disease. Providers can reasonably initiate this therapy but should continue to monitor patients during treatment for any worsening of pulmonary function. More randomized control trials with diverse and large patient samples with direct patient data are needed to strengthen the evidence.

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