EDITORIAL

Beta-Blockers in COPD — A Controversy Resolved?

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Cardiovascular disease, which is common in patients with chronic obstructive pulmonary disease (COPD), has a profound effect on morbidity and mortality,[1] yet the condition is often unrecognized and as a result is undertreated.[2] Systematic reviews have recognized the underuse of beta-blockers in patients with COPD who have coexisting cardiovascular disease because of fear of worsening lung function.[3]

Beta-blockers have positive effects on morbidity and mortality in patients with heart failure and in those who have had a myocardial infarction.[4,5] Most retrospective observational studies have suggested that such positive effects also occur in patients with COPD who have cardiovascular disease.[6,7] Along with their potential cardiac effects, beta-blockers have noncardiac targets with potential beneficial effects in patients with COPD, such as reducing systemic inflammation, the number of goblet cells, and mucus release. Thus, beta-blockers may have beneficial effects in patients with COPD who do not have clear cardiac indications.

In a meta-analysis of 15 retrospective studies involving patients with COPD, those who received beta-blockers had a 28% lower frequency of death and a 38% lower frequency of exacerbation than those who did not receive a beta-blocker.[8] However, most retrospective studies have included a majority of patients with known cardiac indications for beta-blockers. Data are lacking on the possible beneficial effects of beta-blockers in patients with COPD in whom cardiovascular disease has not been diagnosed.

On the basis of these data, current COPD management strategies indicate that beta-blockers should be prescribed in patients with COPD who have cardiovascular indications, even in those with severe COPD.[9] However, there is reluctance to prescribe beta-blockers in patients with COPD even among those with known cardiac disease,[2] despite the findings of studies of cardioselective beta-blockers that showed either no or relatively small decreases in the forced expiratory volume in 1 second (FEV_1) with long-term treatment.[10] Although observational studies are relevant in providing evidence from real-world data on the effects of medications, such studies are subject to bias. Thus, randomized, controlled trials are necessary to resolve the controversy over the potential beneficial effects of beta-blockers in COPD.

Dransfield and colleagues[11] now report in the *Journal* the effects of a beta-blocker on the prevention of exacerbations in patients with moderate or severe COPD. In the BLOCK COPD (Beta-Blockers for the Prevention of Acute Exacerbations of Chronic Obstructive Pulmonary Disease) trial, patients with COPD were randomly assigned to receive a beta-blocker (extended-release metoprolol) or placebo, with a primary outcome of the first exacerbation of COPD. The trial was stopped early because of the futility of achieving a salutary outcome for the primary end point. This finding, accompanied by a potential safety signal with respect to exacerbations, sealed the trial's fate. There was no between-group difference in the time until the first exacerbation or in the overall rate of exacerbation. However, among the patients who received metoprolol, there was a greater risk of severe exacerbation (leading to hospitalization) and very severe exacerbation (leading to intubation and mechanical ventilation). Although the FEV_1 was similar in the two groups, there was a greater increase in a score for breathlessness in the metoprolol group, which suggests an adverse

effect of the drug on COPD symptoms. There were more deaths in the metoprolol group, although this result should be treated with caution because of the wide confidence interval around the point estimate.

What do the results of this trial mean for the use of beta-blockers in COPD? In answering this question, it is important to understand the clinical composition of the trial population: patients with COPD who did not have overt cardiovascular disease and thus did not have an indication for treatment with a beta-blocker. This population contrasts with the patients in most observational studies that have shown positive effects of beta-blockers in patients with COPD who had an indication for treatment with a beta-blocker. The patients in the BLOCK COPD trial were also at high risk for exacerbation and had at least one exacerbation during the preceding year. Moreover, the patients were at risk for a moderate or severe exacerbation, with more than 50% who had visited an emergency department or been admitted to a hospital during the preceding year. All the patients had moderate or severe airflow limitation but also had other indicators of severity, in that 40% of the patients had chronic respiratory failure and were receiving long-term oxygen therapy.

Thus, the results of this trial are applicable to patients who do not have a therapeutic indication for treatment with a beta-blocker and who have severe COPD with a high risk of severe exacerbations. The trial does not provide any support for the use of beta-blockers in such patients for the prevention of an exacerbation of COPD. There is little evidence that beta-blockers are currently prescribed for this indication. On the contrary, there is good evidence that physicians are still reluctant to prescribe beta-blockers even in patients with COPD who have proven cardiac indications. The results of this trial should not deter the use of beta-blockers in patients with COPD who have cardiovascular indications, with the caveat that the risk–benefit ratio should be considered carefully in patients with very severe COPD at high risk for severe exacerbation.

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