Beta-Blockers: A Tale of Triumphs, Trials, and Tribulations

The discovery of beta-adrenergic receptor antagonist propranolol by Sir James Black in 1964 was a landmark event in the history of cardiovascular therapeutics.[1] It proved to be the first effective treatment for angina pectoris. Thereafter, the story of these agents, commonly referred to as beta-blockers, is undoubtedly an unparalleled one in the era of modern therapeutics. Beta-blockers became the mainstay of treatment of major cardiovascular diseases (CVDs), including hypertension, angina, myocardial infarction, and arrhythmias, besides being used for an array of noncardiovascular indications. The events took a dramatic turn for these versatile agents with the turn of the century when the landmark MERIT–HF trial, the CIBIS–II trial, and the COPERNICUS trial paved way for the use of beta-blockers in heart failure – a hitherto absolute contraindication.[2,3] This particular indication of a selected group of beta-blockers (carvedilol, metoprolol, bisoprolol, and lately, nebivolol) took the medical world by storm prompting Cruickshank to observe "beta-blockers continue to surprise us."[4] The tale of beta-blockers' utility in clinical conditions where these agents were deemed contraindicated, going by the rationale of their mechanisms, is no less than an enigma in itself.

Egged upon by such observations, an increasing volume of literature has accumulated about the utility of beta-blockers in patients of chronic obstructive pulmonary disease (COPD), despite their potential to exacerbate the condition. Studies suggest that the use of selective beta-blockers do not result in adverse respiratory effects among patients with COPD and that selective beta-blockers can be cautiously prescribed for patients with COPD and CVD.[5-7] It is to be noted that most of these patients had concomitant CVD. However, literature suggests that beta-blockers are underused in such patients as the fear of exacerbating the condition due to worsening lung function looms large.

The major chunk of evidence on the use of beta-blockers in COPD comes from observational studies. A recent retrospective cohort study reported 10,638 patients hospitalized with the diagnosis of acute myocardial infarction (AMI) and received beta-blockers, of whom 5136 (48.3%) used cardioselective beta-blockers, 5502 (51.7%) used nonselective beta-blockers, and 95 (0.9%) patients used both selective and nonselective beta-blockers. The authors concluded that the use of beta-blockers was associated with a lower mortality rate in patients with COPD after AMI and did not increase the risk of COPD.[8] Some studies have shown that beta-blockers decrease the risk of acute exacerbation of COPD. A meta-analysis of 15 retrospective studies involving patients of COPD showed that beta-blockers use resulted in a significantly lower frequency of exacerbation of COPD and death as compared to those who did not get these drugs (38% and 28%, respectively).[9] Another study reported a decrease in exacerbations of COPD in patients on beta-blockers.[10] However, most data come from patients who had co-existing cardiovascular conditions for which beta-blockers were indicated, whereas the data on the use of beta-blockers in patients of COPD without CVD are lacking. Moreover, being observational studies, the inherent limitations of bias by immeasurable and unrecorded confounding factors cannot be overlooked.

The proposed mechanisms of the useful effects of beta-blockers in COPD patients come from animal studies, which reported that administration of beta-blockers increased the density of pulmonary β2-adrenergic receptors due to their up-regulation. Other mechanism may include beta-blocker-induced reduction of sympathetic tone, inhibition of cardiac stimulation by catecholamines, and increased production of nitric oxide in vascular smooth muscle.[11,12] These agents are also proposed to reduce systemic inflammation and mucus release.

A recent study by Dransfield *et al*. reported the effects of metoprolol on prevention of acute exacerbations in patients of COPD in the Beta-blockers for the Prevention of Acute Exacerbations of COPD Trial.[13] It was a multicenter, prospective randomized, placebo-controlled trial in which 532 COPD patients without a history of CVD and not receiving prior beta-blockers were assigned to extended release metoprolol or placebo. The primary end point was the time until first exacerbation of COPD. However, the trial was stopped early – due to futility pertaining to primary endpoint and safety concerns. Metoprolol was associated with a higher risk of exacerbation, leading to hospitalization (hazard ratio, 1.91; 95% confidence interval, 1.29–2.83) with 11 deaths reported as compared to five in placebo group. The trial had its own set of limitations including difficulty in blinding and exclusion of patients on prior beta-blockers. The authors concluded that the time until first COPD exacerbation was similar in the two groups, but metoprolol caused more hospitalization due to exacerbation. The results of this trial indicate cautionary use of beta-blockers for the prevention of exacerbations in patients of COPD who do not require beta-blockers for any cardiovascular comorbidity. Till we have more evidence in this context, the basic principle of benefit-to-risk assessment should be the guiding light while making therapeutic decisions, and till then, the tale of beta-blockers in the therapeutic arena continues.

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