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AF and Obstructive Lung Disease: Don't Fear the Beta-Blocker

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Atrial fibrillation (AF) and obstructive lung disease are both growing public health problems associated with increased mortality.^{1, 2} Notably, patients with AF and obstructive lung disease have higher symptom burden, worse quality of life, and worse cardiovascular and bleeding outcomes.³ Heart rate control is an important component of AF management that improves symptoms and prevents tachycardia-induced cardiomyopathy.⁴ However, older studies of beta blocker (BB) administration in patients with asthma demonstrated acute drops in expiratory volumes and concerns for acute bronchoconstriction due to beta-receptor antagonism.⁵ The results of these studies loom in the mind of prescribing physicians and may sway them to choose an alternative rate control agent when treating patients with obstructive lung disease. The American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines recommend using a non-dihydropyridine calcium channel blocker (CCB) for rate control of AF in patients with obstructive lung disease (Class I, level of evidence C).⁴ Consistent with this recommendation, BBs (a cornerstone of many rate control strategies) are often underutilized in patients with obstructive lung disease.⁶ However, large population studies have demonstrated that rate control of AF with BBs is associated with lower mortality than with CCBs or digoxin.⁷ Moreover, the use of BB in obstructive lung disease is also associated with lower mortality independent of cardiovascular disease and without adverse effect on pulmonary function.⁸ This raises the question: which rate control agents should be used in patients with AF and obstructive lung disease?

In this issue of *HeartRhythm*, You, *et al.* evaluated the impact of different classes of rate-control medications on all-cause mortality in patients with AF and obstructive lung disease. The authors used the South Korean National Health Insurance Database to identify more than 13,000 patients with AF and obstructive lung disease and then analyzed all-cause mortality rates in patients receiving a single drug class (cardioselective BB, non-selective BB, CCB, or digoxin). They found that patients who were rate controlled using cardioselective or non-selective BBs had lower mortality compared to patients receiving CCBs. Additionally, use of digoxin was associated with a higher mortality than CCB use.

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These differences persisted when adjusting for duration of drug use, propensity matching, and in subgroup analyses of comorbidities. The authors concluded that use of both cardioselective and non-selective BBs for AF rate control are associated better survival when compared to CCBs in patients with obstructive lung disease.

The authors' analysis addresses an important clinical question and provides valuable insight. A unique advantage of their database is its inclusiveness, capturing 98% of the Korean population, including medication use and clinical outcomes. The authors conducted multiple analyses to control for imbalances in drug exposure times and covariates (including the severity of the lung disease) which differed between groups and may have influenced rate control agent selection. Across all of these analyses, a consistent pattern emerged: beta-blockade was associated with lower mortality rates and digoxin with higher mortality rates compared to CCBs.

While well designed, the study does have several limitations that are important to consider. First, due to the retrospective, observational nature of the study the findings should be considered hypothesis generating; they cannot demonstrate cause and effect. The authors used propensity score matching to limit the influence of confounding, but propensity techniques can only mitigate confounding due to factors captured in the administrative dataset. Unmeasured clinical variables such as intolerance to drug classes, baseline blood pressure, and heart rate likely influenced the selection of rate control agents and are not accounted for in the current analyses. The authors also limited the analysis to patients treated with a single class of atrioventricular nodal blocking agents and thus reduced the cohort size by 95% (from 267,649 to 13,111 patients). This is a notable limitation since many patients require more than one atrioventricular nodal blocking agent to achieve adequate rate control.⁹ Furthermore, patients who had side effects or intolerance to one drug class and were switched were excluded from the analysis, thus introducing bias. The choice of all-cause mortality as an endpoint is both a strength and weakness of the study. It is an objective and unambiguous outcome; however, it is also influenced by a plethora of factors. Presumably the lower mortality was driven by a lower frequency of cardiovascular events, but the broadness of the outcome impedes a more granular understanding of the influence of each type of atrioventricular nodal blocking agent. Finally, while BBs were associated with lower rates of mortality than CCBs, the impact of rate control agent on respiratory status was not investigated (nor likely feasible in this dataset).

Prior clinical trial data have shown that beta-blockers are the most-effective agents for lowering heart rate in patients with AF.¹⁰ Now, data from the South Korean National Health Insurance Database provide an intriguing signal that use of BBs for rate control may result in lower mortality when compared with CCB in patients with obstructive lung disease. These data also suggest that digoxin is associated with increased mortality in this population. Prospective, randomized controlled trials, like the ongoing RATE-AF (Rate control Therapy Evaluation in permanent AF; NCT02391337) trial, are required to answer the question of "which treatment is best?" In the meantime, the present study adds to the growing body of literature suggesting that the presence of obstructive lung disease should not dissuade clinicians from using beta blockers; it may be their best option for rate control.

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