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Implications of Aggressive in 'PAH with comorbidities' Therapy: What Does That Mean?

Announcer:
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Dr. Saggar:
Hello, I'm Rajan Saggar from the University of California, Los Angeles. I'm going to speak to the aggressive approach in PAH patients with comorbidities and what that looks like.

For PAH patients with comorbidities, we're specifically referring to cardiopulmonary comorbidities. Over time, it has been appreciated that the demographics and characteristics of PAH have changed. The average age at diagnosis is much higher than in the 80s and 90s, and is now around 60 years of age. And older patients, as we know, are more likely to have comorbid conditions, often raising concern for group 2 and/or group 3 PH.

The definition of comorbidities in group 1 PAH have really produced two emerging clinical phenotypes; one is the left heart phenotype. These are often elderly, female patients with risk factors for preserved ejection fraction heart failure, specifically hypertension, obesity, diabetes, and/or coronary artery disease. And it turns out that 30% of these patients have atrial fibrillation. Again, the so-called left heart phenotype.

Another phenotype that's emerged is the cardiopulmonary phenotype. These are often elderly males with low diffusing capacity, usually less than 50% are predicted, and hypoxemia with either normal or near-normal CT chest imaging, and significant history of smoking cigarettes, as well as risk factors for left heart disease. It turns out that the mortality of the left heart phenotype is very similar to those with PAH, group 1 PAH. And the mortality, interestingly, of the cardiopulmonary phenotype is much lower than the typical PAH patient. Concurrently, there are no evidence-based guidelines for determining a patient's phenotype. So this is a work in progress.

In this population, we gained initial insights regarding PAH with and without comorbidities from the initial AMBITION study, which is where we currently - where we obtained the current recommendation for upfront combination therapy with two oral agents. Initially, in this AMBITION study, there was the inadvertent enrollment of patients with three or more risk factors for preserved ejection fraction heart failure, often with only mild increases in pulmonary vascular resistance. And this was eventually amended during the study at 14 to 18 months into the study, after study enrollment had already begun.

The analyses of the two cohorts, the ex-primary analysis cohort with comorbidities for preserved ejection fraction heart failure, compared to the more traditional PAH patient population without comorbidities, interestingly showed similar direction of favorable outcomes in the primary and secondary endpoints, but with less magnitude. It was also noted that there was an increased frequency of adverse reaction profile, such as edema with an endothelial receptor antagonist, and increased frequency of discontinuation of PAH medication in this ex-primary analysis cohort, which had the comorbidities. But the point here is that patients did improve, and in fact, in this study, there was a 30% improvement in clinical failure rate in the patients who had comorbidities, compared to the 50% improvement in the rate of clinical failure in the typical PAH patient when compared to the pooled monotherapy arms.

Lastly, there's a recent study published from the COMPERA registry, evaluating this 4-strata risk classification, and comparing incident idiopathic PAH with and without risk factors for preserved ejection fraction heart failure. Out of 1,120 idiopathic PAH patients, 81% were without comorbidities and 19% had comorbidities. The median age, as we suggested earlier, was 72 years, again to the point that these patients with PAH are older in the current era. The Cox proportional hazard modeling showed male gender, higher age, higher risk at baseline, lower diffusing capacity, and the number of comorbidities independently associated with mortality. Most patients in this study were treated with a phosphodiesterase-5 inhibitor monotherapy, and up to one-third of patients with comorbidities received dual combination therapy. The conclusions from the study are important that the 4-strata risk classification was able to predict outcomes in idiopathic PAH regardless of the presence of comorbidities. PAH medications improved brain natriuretic peptide, functional class, walk distance, and mortality risk in idiopathic PAH with comorbidities. But as with AMBITION, this was less prominent than in idiopathic PAH patients without comorbidities, but again still improved. More PAH therapy discontinuations and adverse reactions in the idiopathic PAH group with comorbidities was seen, again also similar to what was seen in the AMBITION study.

So, initial therapy - to conclude, initial therapy currently, based on the ERS/ESC guidelines for PAH with comorbidities is monotherapy with either a phosphodiesterase-5 inhibitor or an endothelin receptor antagonist, but that additional PAH-specific therapy should be considered on a case-by-case basis. There is no solid evidence on treatment strategies of elderly PAH patients with comorbidities excluded from clinical trials. Most of the existing clinical experience in this setting in idiopathic PAH patients with comorbidities is with a phosphodiesterase-5 inhibitor drug, and the least experience is with the prostacyclin pathway.

Thank you for listening.

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