Are We Treating Heart Failure in Patients with Chronic Obstructive Pulmonary Disease Appropriately?

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Chronic obstructive pulmonary disease (COPD) and heart failure (HF) share risk factors and comorbidities. These include smoking, coronary artery disease, diabetes, hypertension, and atrial fibrillation and often result in the two diseases coexisting in the same patient (1) (Figure 1). HF can be of the preserved ejection fraction (HFpEF) and reduced ejection fraction (HFrEF) varieties, with HFpEF predominating in patients with COPD (2). Both COPD and HF can present with similar signs and symptoms, especially dyspnea and reduced exercise capacity. Additional challenges in diagnosing and treating COPD with HF include difficulties with HFpEF diagnostic criteria, medication regimens that potentially impair optimal outcomes for the other disease, and the tendency to undertreat cardiovascular disease in the setting of COPD. All of these factors have the potential to worsen patient outcomes and increase healthcare costs. Therefore, it is important to know how often these diseases coexist, what effect recommended treatments of COPD and HF have had on the patient with COPD and HF, and whether outcomes have improved in recent years.

In this issue of *AnnalsATS*, Axson and colleagues (pp. 939–948), in a very detailed and scholarly assessment, explore data derived from the Clinical Practice Research Datalink in the United Kingdom from 2006 to 2016 (covering ~6.9% of the entire UK population) (3). The authors focus on the impact of incident or new HF on COPD mortality. To meet the definition of COPD in the study, patients had to be at least 35 years old at COPD diagnosis, have a history of smoking, and have airflow obstruction as evidenced by a forced expiratory volume in 1 second (FEV_1)/forced vital capacity ratio less than 0.70. To meet the definition of HF, patients had to have had their first occurrence of an HF diagnostic code in primary care during the study period (2006–2016). There was no echocardiographic or biomarker (e.g., brain natriuretic peptide) corroboration. The authors identified 95,987 subjects with COPD using the definition above within the time window of interest (~10 yr). Among that group, 4,862 (~5%) developed incident HF, and 91,125 (95%) did not. The authors then examined the effect of incident HF on all-cause mortality using data from the Office for National Statistics in the United Kingdom.

This analysis showed that the crude incidence of HF in the COPD population was essentially stable from 2006 to 2016 (~1.18 per 100 person-years; 95% confidence interval, 1.09–1.27). Importantly, HF dramatically increased the 1-year mortality threefold and doubled both the 5- and 10-year mortality compared with COPD without incident HF. Finally, the authors report that the adjusted mortality rate ratios for incident HF, taking into account age, sex, body mass index, Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage, smoking status, history of coronary artery disease, and diabetes, did not improve over time in examination of the years 2006, 2011, and 2015.

Why such excess mortality in patients with incident HF and COPD, especially in the first year? As Baldwin, Cournand, and Richards asserted in the 1940s and Graham Barr recently reiterated, "[F]unctionally, it is obvious that the pulmonary and circulatory apparatus are one unit," and the combination of heart and lung pathology creates additive and unique pathophysiology (4, 5). Several mechanisms may be at play in this interaction of these diseases and the observed increase in mortality, including *1*) hyperinflation from gas trapping that reduces the volume available for cardiac filling and thus reduces cardiac output, *2*) pulmonary hypertension worsening right ventricular function, *3*) ventricular interdependence from pressure or volume overload, *4*) hypoxic vasoconstriction and vasculopathy, *5*) abnormal ventilation–perfusion relationships, and *6*) hypoxemia (6, 7).

Are there medication regimen choices, such as β-agonists or β-blockers, that potentially increase mortality in this combined HF and COPD group? Clearly, β-blockers have been shown to improve outcome and reduce mortality in HF with reduced ejection fraction (8, 9), although they are chronically underused when COPD is present (10, 11). Is this underuse justified? A recent trial of the cardioselective β-blocker metoprolol did not show any adverse effect on FEV_1 (12), and cardioselective β-blockers are recommended in the presence of comorbid

DOI: 10.1513/AnnalsATS.202004-395ED

Ann Am Thorac Soc Vol 17, No 8, pp 932–938, Aug 2020
Internet address: www.atsjournals.org

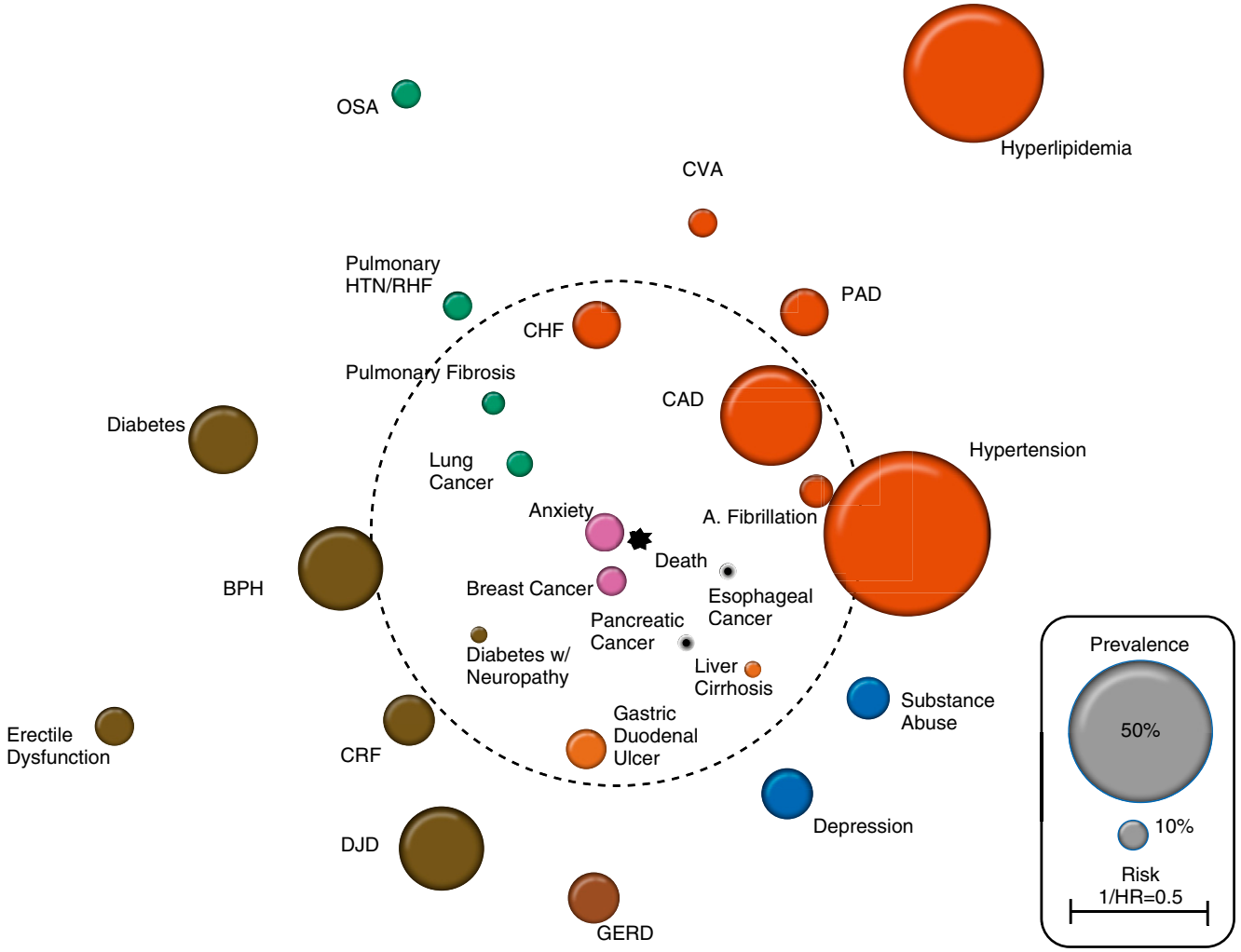

Figure 1. A total of 1,664 subjects with chronic obstructive pulmonary disease (COPD) were followed for a mean of 51 months with COPD and various comorbidities (average, 6 ± 3). Forty percent of the subjects died. Divo and colleagues (1) developed a "comorbidome" to graphically express comorbidities with more than 10% prevalence in the entire cohort and demonstrate those with the strongest association with mortality (hazard ratio [HR], >1; 95% confidence interval, >1; $P < 0.05$). The area of the circle relates to the prevalence of the disease. The proximity to the center (mortality) expresses the strength of the association between the disease and risk of death. This was scaled from the inverse of the HR (1/HR). All bubbles associated with a statistically significant increase in mortality are fully inside the dotted circle (1/HR, 1). Bubble colors represent organ systems or disease clusters (cardiovascular = red; female-specific comorbidities = pink; pulmonary = green; psychiatric = blue; others = brown and orange). Importantly, congestive heart failure (CHF) and other comorbidities are within the strong association circle. A. fibrillation = atrial fibrillation/flutter; BPH = benign prostatic hypertrophy; CAD = coronary artery disease; CRF = chronic renal failure; CVA = cerebrovascular accident; DJD = degenerative joint disease; GERD = gastroesophageal reflux disease; OSA = obstructive sleep apnea; PAD = peripheral artery disease; pulmonary HTN/RHF = pulmonary hypertension and right heart failure. Reprinted from Reference 1.

COPD and HFrEF (13). Perhaps provider reticence to use evidence-based therapies for HFrEF when COPD is present may partially explain the lack of reduction in adjusted mortality rates in this study. Finally, because HFpEF is the more common phenotype in COPD and has had relatively disappointing therapeutic trial results to date (14) with respect to improved outcomes or reduced mortality (15), one would not expect current medication regimens (primarily diuretics) to have had a positive effect on the mortality rates in this study. Interestingly, there is some recent interesting data indicating that β-agonists may improve pulmonary hemodynamics in HFpEF (16).

Regarding the types of deaths observed in this study, respiratory diseases were most prevalent (~40%), with circulatory diseases representing approximately 35% and neoplasms about 11%. These proportions were true in both the 2006–2010 and 2011–2016 time frames and did not appear to be significantly affected by GOLD status (1–2

vs. 3–4). The results of the study by Axson and colleagues can be compared with the mortality data collected as part of the very large COPDGene (COPD Genetic Epidemiology) study in the United States by Young and colleagues (17) over a similar time period. The latter study included 8,157 current or former smokers with at least a 10–pack-year smoking history. Over 7.07 years (57,694 person-years of follow-up), they observed 1,371 deaths. All of these subjects had quantitative computed tomographic (CT) scans of the chest, and the authors classified the subjects as either airway predominant (airway thickening as measured by wall area percentage), emphysema predominant (high percentage emphysema as measured by percentage of area below −950 Hounsfield units), both, or neither. In the airway-predominant group, approximately 40% died of respiratory diseases, 24% died of cardiovascular diseases, and 21% died of neoplasms. The emphysema group had higher respiratory mortality (47%), lower cardiovascular mortality (8%), and higher neoplasm mortality (29%). When both these CT scan characteristics were present, respiratory mortality increased to 67%, with only 7% being related to cardiovascular causes and 14% to neoplasms. When neither of these CT scan abnormalities were present, respiratory mortality was very low (8%), cardiovascular mortality was 24%, and neoplasm mortality was 34%. These CT scan data are interesting in that the highest risk for cardiovascular mortality was in the airway-predominant group. Lacking CT scan data, the study of Axson and colleagues cannot provide information regarding COPD phenotyping in determining cardiovascular versus respiratory risk of death.

The strengths of the study of Axson and colleagues include the use of one of the world's largest longitudinal databases and the linkage to mortality data from the same population (essentially 100% linkage covering 6.9% of the entire UK population). Issues that are more difficult to quantify and compensate for are the potential errors in diagnosis and coding, the use of an administrative rather than a clinical database, the lack of laboratory biomarkers or quantitative assessment of cardiac function that would have augmented the precision in the analysis (e.g., HFpEF vs. HFrEF), and the lack of quantitative CT chest imaging.

What can we learn from these data? First, HF incidence is certainly higher in older patients, males, and patients with advanced COPD (GOLD 3–4). We need to keep in mind that these diseases frequently coexist and bring to bear diagnostic strategies that separate pulmonary from cardiovascular etiologies of the patient's sign/symptom complex, especially dyspnea and exercise limitation. Second, among patients with COPD, HF tripled mortality at 1 year and doubled mortality at 5 and 10 years relative to patients who did not have incident HF; we clearly need to improve our vigilance and therapy in this vulnerable group and create evidence-based therapeutic guidelines. Finally, despite improvements in HF recognition and treatment, the mortality outcomes of patients with COPD and HF did not appear to improve across time in this study. This is perhaps the most perplexing of all, because the medical establishment does not seem to be "moving the dial" in this area. Resolving this mystery should be the subject of further research. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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