not only identified a novel genetic risk factor for ARDS, but also provided evidence for a potential mechanism resulting in the altered risk.

The most significant limitation to the study conducted by Wei and colleagues[8] is that the only causal mediator evaluated was a single measure of platelet count at ICU admission. Based on these data, it is difficult to determine whether the effects of platelet count on ARDS risk are a result of decreased platelet production or increased platelet activation, lung sequestration, and consumption. Additionally, platelet function may be equally as important in mediating ARDS risk as platelet count and may explain why count was only a partial causal mediator of the *LRRC16A* and ARDS association. In addition to validating their findings in an independent population, future research should evaluate the effects of *LRRC16A* on measures of platelet consumption and production, such as serial platelet counts or immature platelet fractions, as well as measures of platelet function, aggregation, and neutrophil adhesion.

Despite these limitations, Wei and colleagues[8] have successfully identified a variant in *LRRC16A* associated with altered ARDS risk, at least partially mediated via effects on platelet count. *LRRC16A* encodes the protein, capping protein ARP2/3 and myosin-I linker (CARMIL), important in actin-based cellular processes.[14] This protein has not previously been implicated in ARDS, and the mechanisms underlying its effects on platelet count are not completely understood. Furthering our understanding of the role of *LRRC16A* and CARMIL protein in platelet development and/or function as well as ARDS pathogenesis may identify novel therapeutic targets within platelet cellular processes with relevance to ARDS. Likewise, *LRRC16A* variation may represent a key focus for pharmacogenetic interaction in ongoing trials of aspirin therapy. Therefore, the study by Wei and colleagues[8] provides key data to focus our near-term research efforts on the role of platelets in ARDS.

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COPD in Heart Failure

Are There Long-term Implications Following Acute Heart Failure Hospitalization?

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Heart failure (HF) and COPD are major and increasing public health problems worldwide. In the United States, HF affects >5 million adults and results in >1 million hospitalizations annually.[1] Despite advances in the treatment of chronic HF, outcomes following acute HF hospitalization remain poor.[1] Given the neutral results of most recent HF trials, there is a need for a critical reappraisal of strategies to improve outcomes.[2] COPD affects >15 million Americans, commonly occurs in patients with HF, and is associated with significant morbidity and mortality.[3-5] Recognition of the impact of

comorbid conditions such as COPD on the characteristics and outcomes of patients with HF may represent a first step to identify strategies to improve outcomes.[6] It is in this context that Fisher et al[7] assessed the patient phenotype, management, and long-term outcomes of hospitalized patients with HF and COPD in this issue of *CHEST* (see page 637).

Fisher et al[7] report the results of an observational study of 9,748 patients with acute HF hospitalized at 11 medical centers in Massachusetts during 1995, 2000, 2002, and 2004 with follow-up through 2010. They compared patients with HF with and without COPD with respect to baseline characteristics, HF medication use, and all-cause mortality. The investigators identified HF hospitalizations by coding data with confirmation based on Framingham criteria. Patients with both preserved and reduced ejection fraction were included. Comorbid COPD was defined by clinical or radiographic evidence without further details related to pulmonary function testing or COPD medications. Approximately 35% of patients with acute HF had COPD with a stable prevalence over the study. Patients with COPD had more comorbidities such as renal disease, anemia, and atrial fibrillation compared with patients who did not have COPD. Despite increases in the use of β-blockers over time in those with and without COPD, patients with COPD remained comparatively undertreated (58% vs 73% use in 2004). On multivariable analysis, COPD was associated with similar in-hospital and 30-day mortality, but was associated with a 10% increase in 1-year mortality and a 40% increase in 5-year mortality. When comparing patients identified in 1995 to those from 2004, long-term outcomes improved over time in both groups. However, the magnitude of the survival improvement was greater in patients without COPD.

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This population-based investigation adds to the growing literature describing the intersection of HF and COPD. The strengths of the analysis include the large sample size, community-based perspective, and robust collection of long-term outcomes. The data add incremental insight into the impact of COPD in patients with HF in routine clinical practice outside the context of registries[8] and clinical trials.[9,10] Similar to previous reports, this study demonstrates comparable short-term outcomes in patients with and without COPD, but worse long-term outcomes with COPD.[8,11,12] The present study extends previous results by demonstrating that the risk associated with COPD increases significantly over time out to 5 years following acute HF hospitalization. The 40% increase in all-cause mortality at 5 years independently associated with COPD is striking. Moreover, the finding of undertreatment with β-blockers in patients with COPD despite temporal increases in use highlights a key area for quality improvement. The use of β-blockers at discharge was fairly low in this HF cohort with COPD (58%) even when compared with registry data from a similar time period. For instance, in an analysis of HF patients with reduced ejection fraction and COPD in the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF) registry, there was 52% β-blocker use on admission for acute HF and 66% use on discharge.[8] Thus, use of β-blockers in routine clinical practice in the setting of concomitant COPD may be worse than previously recognized. Contemporary data are required to characterize current uptake of β-blocker use.

There are several limitations in the present work, which are, in general, clearly identified by the authors. Despite the large sample size, the population was mostly white and the generalizability of these findings to other populations is unclear. There are several other characteristics of the COPD population that are different compared with earlier analyses.[8] For instance, while the patients with COPD had increased renal dysfunction based on medical history, their creatinine values were lower compared with those without COPD. The specific reasons for these findings are unclear, but may be related to inherent limitations in the setting of observational analyses. Along these same lines, the definition of COPD in this cohort is limited based on the acquisition of data from chart review. While this definition is similar to that used in previous studies, the lack of pulmonary function testing data and pulmonary medications limits the understanding of pulmonary

disease severity and management. Future studies could benefit from a COPD definition that incorporates a standardized physician assessment of disease signs and symptoms, smoking and prior pulmonary related hospitalizations, imaging and biomarker data, and clinical response to disease-specific therapies. Additionally, long-term follow-up data on outpatient medications and cause of death would be informative.

In terms of clinical application, this study highlights the importance of assessing for and recognizing pulmonary disease in patients with HF. Because HF and COPD can present with similar symptoms, a multidisciplinary care team may be beneficial for these complex patients. There is increasing evidence that the use of β-blockers in many patients with HF and COPD is safe and efficacious.[10,13-16] Despite these data, providers are still withholding β-blockers in patients with COPD likely due in part to concerns about precipitating pulmonary exacerbation. Importantly, there is a mechanistic rationale to preferentially use cardioselective agents such as metoprolol succinate or bisoprolol rather than carvedilol[17] and several small studies support this approach.[18-20] However, observational studies have also suggested that there is no differential benefit with cardioselective compared with noncardioselective β-blockers.[10,16] Thus, one approach is to preferentially use cardioselective agents, but if these are not tolerated for various nonpulmonary reasons, it may be reasonable to try the noncardioselective agent carvedilol. Ultimately, an adequately powered randomized-control trial of different β-blocker and bronchodilator therapies in patients with HF and COPD is warranted.[21] Increasing awareness of the burden of these comorbid illnesses and dedication to further research in this area may lead to improved patient outcomes.

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