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EDITORIAL COMMENT

Impact of Pneumonia in Heart Failure Patients*

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In light of the COVID-19 pandemic, the risks and consequences of pneumonia have never been more apparent than during this past year. Although poor outcomes have been well-documented in patients with heart failure and COVID-19 (1), other causes of pneumonia are a known source of increased morbidity and mortality in this population. Previous studies have shown that infection is a common cause of hospitalization in patients with heart failure, and pneumonia is associated with increased risk of mortality in patients who are hospitalized (2,3). Pneumonia can also contribute to the development of heart failure. As the prevalence of heart failure continues to rise (4), exploration of factors that contribute to poor outcomes is of utmost importance.

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In this issue of the *Journal*, Shen et al. (5) present a retrospective analysis of the incidence of investigator-reported pneumonia in patients enrolled in the PARADIGM-HF (Prospective Comparison of Angiotensin Receptor-Neprilysin Inhibitor With Angiotensin-Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure) (6) and PARAGON-HF (Prospective Comparison of ARNI [Angiotensin Receptor-Neprilysin Inhibitor] With ARB [Angiotensin Receptor Blocker] Global Outcomes in Heart Failure With Preserved Ejection Fraction) (7) trials. In PARADIGM-HF, sacubitril/valsartan, an angiotensin receptor blocker/neprilysin inhibitor, was shown to be superior to enalapril in reducing the risk of death and heart failure hospitalization in patients with heart failure with reduced ejection fraction. The investigators found that 6.3% of patients enrolled in this study developed pneumonia after randomization, with an incidence rate of 29 per 1,000 patient-years (95% confidence interval [CI]: 27 to 32 per 1,000 patient-years). Expectedly, those who developed pneumonia were more likely to have chronic obstructive pulmonary disease (25.6% vs. 12.0%), diabetes (42.6% vs. 34.1%), atrial fibrillation (45.6% vs. 36.2%), higher N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and lower estimated glomerular filtration rates (eGFR) than patients who did not. The development of pneumonia was associated with a substantially increased of risk of death from any cause, with an adjusted hazard ratio (HR) of 4.34 (95% CI: 3.73 to 5.05). Its counterpart, PARAGON-HF, which compared sacubitril/valsartan to valsartan alone in patients with heart failure with preserved ejection fraction, did not demonstrate a significant reduction in total heart failure hospitalizations and death from cardiovascular causes, although it narrowly missed its primary composite endpoint. In PARAGON-HF, 10.6% of the total cohort developed pneumonia, with an incidence rate of 39 per 1,000 patient-years (95% CI: 36 to 42 per 1,000 patient-years). Similar to the PARADIGM-HF cohort, those patients in PARAGON who developed pneumonia also had higher rates of comorbidities, including chronic obstructive pulmonary disease (26.2% vs. 12.5%), diabetes (48.6% vs. 42.3%), atrial fibrillation (61.4% vs. 51.5%), higher NT-proBNP levels, and lower eGFR. Again, the development of pneumonia was associated with an increased risk of death from any cause, with an adjusted HR of 3.76 (95% CI: 3.09 to 4.58). In both

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cohorts, those who developed pneumonia reported lower Kansas City Cardiomyopathy Questionnaire clinical summary scores, and those in PARAGON-HF reported a worse New York Heart Association functional class.

The current study had a number of limitations. First, it was a post hoc analysis, and pneumonia was not a pre-specified endpoint in either trial. As such, there were no clinical criteria by which patients were diagnosed, no adjudication of these events, and no available data regarding the methods of diagnosis, severity, culture or serology results, and treatment. It was also unknown as to what proportion of events were related to community exposure rather than hospital acquired, although patients reported to have aspiration pneumonia were excluded from analysis. This was an important distinction because the prevention, treatments, and outcomes could differ significantly. Rather, patients with pneumonia were identified by reviewing investigator-reported adverse events and including any cases coded as "pneumonia." Although the diagnosis of pneumonia can be straightforward in patients with pre-existing cardiopulmonary disease, it can often be difficult to differentiate between clinical pneumonia and pulmonary edema on the basis of clinical and radiographic evaluation. It has been suggested that patients with heart failure are often treated with antibiotics when the diagnosis of pneumonia is uncertain (8). The investigators speculated that investigator-reported pneumonia events were unlikely to have represented missed heart failure decompensations, because there was no association between administration of sacubitril/valsartan and incidence of pneumonia. If reports of pneumonia were due to heart failure events, it was expected that there would have been a reduction in the group receiving sacubitril/valsartan, which was not observed. Although logical, this conclusion is probably not statistically valid.

To evaluate whether general infection in and of itself was associated with worse outcomes, the investigators chose the only other adverse event that was sufficiently powered for analysis as a comparator group—urinary tract infection. They found that urinary tract infection was reported in 395 (4.7%) patients in PARADIGM-HF and 579 (12.1%) patients in PARAGON-HF, with rates of 22 per 1,000 patient-years (95% CI: 20 to 24 per 1,000 patient-years) and 45 per 1,000 patient-years (95% CI: 41 to 49 per 1,000 patient-years), respectively. Many of the variables associated with pneumonia were also associated with urinary tract infections, including older age and comorbidities (e.g., diabetes and chronic obstructive pulmonary disease). As in patients reported to have pneumonia, the risk of death (from any cause or cardiovascular) was higher in patients with urinary tract infections, although to a lesser degree than pneumonia. Because these were also investigator-reported events and not pre-specified, there did not appear to have been universal diagnostic criteria. In addition, data regarding the severity of infection and treatments were not available, making it difficult to generalize these findings. Nonetheless, it further suggests the increased risk posed by common infections in patients with heart failure.

Because clinical trial study populations often have a lower comorbid disease burden than those in the community, the investigators speculated that the development of pneumonia carried an even greater risk for those with heart failure than these data suggest, although the rates observed in this study were comparable to those observed in similar age groups with heart failure (9).

The novel finding of the study was that, although the greatest risk to patients occurred in the month following the acute pneumonia episode, there was a persistent risk beyond 3 months. Acutely, increased alveolar fluid in heart failure could impair bacterial clearance and affect local defense mechanisms, resulting in pneumonia, but previous research also implicated dysregulation of inflammatory pathways and decreased nitric oxide production with resulting endothelial dysfunction (10). This persistence of an elevated inflammatory state might contribute to the development or worsening of heart failure symptoms (11) and might explain why persistently worse outcomes were seen in this study even after patients had recovered from the acute pneumonia event. However, what was not clear from their data was whether the pneumonia led to the increased risk or whether it was the consequence of the higher risk profile of the patients who developed pneumonia. The investigators did attempt to adjust for various risk factors using multivariable analysis and still found worse long-term effects.

Whether treatment of chronic inflammation would be a potential treatment strategy remains purely speculative, and therefore, the investigators focused on a tried and true preventive strategy for pneumonia (i.e., vaccination). For the most common community-acquired bacterial pneumonia, *Streptococcus*, routine vaccination is recommended for all adult patients with heart failure. Likewise, annual vaccination for seasonal influenza is also recommended. Despite these recommendations, a significant number of patients with heart failure remain unvaccinated (12).

Although data exist to suggest significant cardiovascular risk reduction with influenza vaccination (13), including a previously published study of the PARADIGM-HF cohort (14), high-quality evidence regarding the benefit of vaccination in patients with heart failure is limited and somewhat contradictory. Although aforementioned studies exist to suggest a protective effect of vaccination, others have not shown benefit. For example, Bhatt et al. (12) performed a retrospective review of pneumococcal and influenza vaccination rates among hospitalized patients at centers participating in a large heart failure registry over 5 years. They observed no difference in all-cause mortality between those who received pneumococcal and influenza vaccinations than those who did not (12). It has been suggested that the humoral and cellular response to the influenza vaccine maybe suboptimal in patients with heart failure, and that delivery of a higher dose of trivalent formulation of the vaccine can improve the immune response (15). However, a recent randomized clinical trial of patients with high-risk cardiovascular disease comparing the typical dose of the new standard quadrivalent formulation to the high-dose trivalent form found no difference in hospitalization for cardiovascular or pulmonary cause or death from any cause. Whether higher vaccination rates and newer technology can improve outcomes in this group of patients remains to be seen (16).

As nations around the world race to control the spread of the latest novel respiratory pathogen, this study serves as an important reminder of the ever-present risk posed by pneumonia in patients with heart failure. Evidence continues to mount that the severity of heart failure symptoms and presence of common comorbidities also contribute to this increased risk, suggesting that aggressive optimization of guideline-directed medical therapy and management of comorbidities may be beneficial. The interactions between cardiovascular and pulmonary disease are also complex, and further study is required to better understand the mechanisms by which pneumonia contributes to such increases in morbidity and mortality. Although vaccination alone appears unlikely to be a panacea, it is a readily accessible tool for mitigating disease severity and improving outcomes. After all, an ounce of prevention is worth a pound of cure.

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