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EDITORIAL COMMENT

Can 2 Pills a Day Keep Readmission Away?

Sacubitril/Valsartan to Reduce 30-Day Heart Failure Readmissions*

Robert J. Mentz, MD, Emily C. O'Brien, PhD

Patients with heart failure (HF) routinely experience a course punctuated by recurrent hospitalizations. Following acute HF hospitalization, nearly 30% of patients are rehospitalized within 60 to 90 days (1). Approximately 45% of these hospitalizations are for recurrent/refractory HF symptoms, but a similar percentage is due to noncardiovascular causes (2). Because readmissions worsen patients' quality of life (3), increase the risk for future adverse events (4), and constitute a substantial financial burden (5), interventions that reduce hospitalizations represent an unmet need that would benefit patients with HF, the medical community, payers, and society.

Public and private payers have targeted the reduction of readmissions as a pay-for-performance quality measure. In 2009, the Centers for Medicare & Medicaid Services began public reporting of HF readmission rates and then enacted financial penalties for poorly performing hospitals in 2010 (6). Although data suggest that many early readmissions may be preventable, most interventions targeting reduced readmissions have been ineffective (7). As a result, even with public reporting and financial penalties, incremental improvements in readmission rates have not been observed (8).

Fortunately, additional evidence-based medical therapies for patients with HF with reduced ejection fraction have become available in recent years (9,10). In PARADIGM-HF, sacubitril/valsartan was shown to be superior to enalapril with a 21% reduction in HF hospitalization (10). Additional recent data have shown that the reduction in HF hospitalization from sacubitril/valsartan occurs within the first 30 days of therapy with a long-term benefit on total HF hospitalization burden compared with enalapril (11).

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In this context, Desai et al. (12) present data from PARADIGM-HF assessing the association between sacubitril/valsartan and 30-day readmissions following HF hospitalization in this issue of the *Journal*. The authors extend the results from the primary publication (10) and the recent clinical progression data (11) by focusing on the 30-day period following HF hospitalization. They assessed rates of 30-day all-cause and HF-specific readmission by treatment arm following 2,383 investigator-reported HF hospitalizations (i.e., multiple hospitalizations per patient were used). They observed a 26% risk reduction in 30-day all-cause readmissions and a 38% reduction in HF readmission with sacubitril/valsartan compared with enalapril. Consistent findings were observed when assessing the risk reduction through 60 days, after first HF hospitalizations, and when only adjudicated HF hospitalizations were used as the anchor point for subsequent risk. Two additional subgroup analyses explored readmission risk by patient age (<65 years vs. ≥65 years) and enrolling region (United States vs. non-United States). In general, results were similar in these subgroups despite a low event count in the United States (52 total readmissions, 27 HF readmissions). Interestingly, there was a suggestion that the magnitude of sacubitril/valsartan benefit might be greater on HF-specific readmission in older patients (53% reduction vs. 18% reduction in all-cause readmission) and greater on all-cause readmission in younger patients (35% reduction vs. 17% reduction in HF-specific readmission).

This is a clinically relevant analysis that provides important data supporting the use of

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sacubitril/valsartan to reduce readmissions in patients with HF with reduced ejection fraction. The overall consistency of the results when data were assessed multiple ways supports the robust nature of these findings. The observation of a potential differential effect on rehospitalization type based on age group is interesting. Although these results may be caused by statistical chance when assessing multiple subgroups, they may offer insights into the underlying mechanisms by which sacubitril/valsartan benefits patients with different phenotypes. Future work within the PARADIGM-HF dataset may help to better understand these observations by assessing sacubitril/valsartan's effects on different cardiovascular and noncardiovascular causes for readmission and outcomes by patient age and comorbidity profile.

This study carries with it an important limitation inherent to analyses of treatment effect for events occurring subsequent to the primary event of interest; in this case, readmission following initial HF hospitalization. Because the study population is, by design, restricted to those patients who experienced a first event (17.3% of PARADIGM-HF), the population now exists as an observational cohort rather than a randomized sample. Although results from observational studies can contribute meaningful information, application of appropriate adjustment methods and cautious interpretation of results are critical to valid conclusions. In the present study, the authors examined the respective distributions of baseline characteristics by sacubitril/valsartan and enalapril and did not perform adjustment after observing "no significant treatment-related differences" between groups. However, the power of randomization lies in balancing not just measured but also unmeasured characteristics across treatment arms, and comparable distributions of observed patient characteristics in nonrandomized treatment groups does not exclude the possibility of residual confounding.

In this scenario, any unmeasured factor that affects initial hospitalization and readmission can introduce collider stratification bias (13), a special form of selection bias that occurs when subsetting a population on a common effect of both exposure and outcome. Because of the significant reduction in hospitalization with sacubitril/valsartan observed in the overall PARADIGM-HF trial, it is reasonable to expect that the patients who were hospitalized despite being randomized to the superior therapy (sacubitril/valsartan) may have other important differences compared with those who were hospitalized in the enalapril arm. Failing to adjust for these differences introduces the same bias in a subanalysis of randomized trial data as it does in a nonrandomized comparative effectiveness study.

To truly answer the question of whether sacubitril/valsartan reduces HF readmission, future studies could use a SMART (Sequential, Multiple Assignment, Randomized Trial) design (14), in which patients are rerandomized at key decision points during follow-up, such as readmission. Of course, rerandomization introduces an additional layer of cost and operational complexity, which should be carefully weighed against the benefits of evaluating unbiased treatment effects on recurrent events. Because it is uncertain as to whether such a SMART study will ever be performed with sacubitril/valsartan, the present data provide some support regarding the use of sacubitril/valsartan to reduce readmission.

These observations may not be generalizable to patients with HF who do not meet the PARADIGM-HF entry criteria. Specifically, the trial population represented a subset of the population with chronic HF with reduced ejection fraction able to tolerate relatively high doses of enalapril and then sacubitril/valsartan before randomization. Although the study results are encouraging, it is unknown whether similar results would be seen in those with less clinical stability and/or more advanced HF characterized by hypotension and renal dysfunction. Finally, these data do not apply to approximately 50% of the HF population with preserved ejection fraction.

In conclusion, although sacubitril/valsartan has not been specifically evaluated in the acute HF setting, the post-hospitalization period following clinical stabilization may be an ideal time to initiate the therapy in engaged patients. Through care delivery that uses comprehensive discharge planning and patient education with appropriate initiation of evidence-based therapies and early post-discharge follow-up, it may be possible to bend the curve on readmission in patients with HF.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Robert J. Mentz, Duke Clinical Research Institute, PO Box 17969, Durham, North Carolina 27715. E-mail: robert.mentz@duke.edu.

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