PIONEERing the In-Hospital Initiation of Sacubitril–Valsartan

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In 2015, sacubitril–valsartan was approved in Europe and the United States as a new therapeutic agent for heart failure with reduced ejection fraction. Approval was based primarily on the results of the PARADIGM-HF trial.[1] In that trial, sacubitril–valsartan was compared with enalapril in clinically stable patients with heart failure. At a median follow-up of 27 months, there was a significantly lower rate of the primary outcome of death from cardiovascular causes or hospitalization for heart failure with sacubitril–valsartan than with enalapril.

Despite the robust evidence of benefit seen in the PARADIGM-HF trial, the adoption of sacubitril–valsartan in clinical practice has been slow.[2] This process does not appear to have been accelerated substantially by the publication in 2016 of an American College of Cardiology–American Heart Association focused guidelines update endorsing the use of this therapy,[3,4] a phenomenon that has also been noted for other new drugs and has been termed "clinical inertia."[5] In the specific case of sacubitril–valsartan, one important factor that has contributed to clinical inertia is the cost of the drug ($4650 per year by one estimate), which has led to delays in hospital formulary approval, restrictive prior-authorization requirements by insurers, and high out-of-pocket expenses for patients.[6]

Another factor that has most likely contributed to the slow adoption of sacubitril–valsartan is implicit in the design of the PARADIGM-HF trial. An important requirement for enrollment in the trial was current clinical stability. Eligible patients entered a two-part run-in phase to show, first, that they could take enalapril at a dose of 10 mg twice daily for 2 weeks without having unacceptable side effects and, second, that they could take sacubitril–valsartan for 4 to 6 weeks (initially at a dose of 100 mg twice daily, which was increased to 200 mg twice daily) without having unacceptable side effects. Patients with acute decompensated heart failure were excluded. Thus, the PARADIGM-HF trial studied sacubitril–valsartan when it was administered to clinically stable patients with heart failure, primarily in the outpatient setting.

However, many physicians are reluctant to initiate treatment with new therapeutic agents in the outpatient setting, and patients are less likely to be adherent to treatments when they are initiated in this way, perhaps because the opportunity to educate the patient on the use and importance of the drug is limited by time constraints in the clinic. Studies have shown that, for beta-blockers and aldosterone antagonists, initiation and adherence were enhanced when these agents were prescribed at the time of hospital discharge.[7,8] Therefore, specific evidence that sacubitril–valsartan could be safely initiated in the inpatient setting would be expected to fill an important gap in our knowledge of the use of this drug.[9]

The PIONEER-HF trial, reported in this issue of the *Journal*, was designed to address this issue.[10] The trial enrolled patients who were hospitalized for acute decompensated heart failure, with enrollment occurring no less than 24 hours and up to 10 days after initial presentation. Patients were not required to have a previous diagnosis of heart failure or to have previously been receiving heart-failure medications, so patients with new-onset heart failure were allowed to be included. Of note, a substantial proportion (36%) of the patients enrolled in the trial were black. The randomized treatment assignment was either sacubitril–valsartan or enalapril, but at lower starting doses than those used in the PARADIGM-HF trial. Patients were treated and followed for 8 weeks.

Given that the goal of the PIONEER-HF trial was to establish the safety and efficacy of sacubitril–valsartan in patients who were hospitalized for acute decompensated heart failure, the choice of primary outcome — the change in the N-terminal pro–B-type natriuretic peptide (NT-proBNP) concentration — seems somewhat unexpected. There was a significantly greater reduction in this biomarker with sacubitril–valsartan than with enalapril (–46.7% vs. –25.3%), but this benefit of sacubitril–valsartan on the NT-proBNP concentration has been seen previously, most notably in an analysis of data from the PARADIGM-HF trial.[11]

The more important and novel observation

from the PIONEER-HF trial is the safety profile of sacubitril–valsartan in the context of acute decompensated heart failure. The trial protocol defined four principal safety measures: worsening renal function, hyperkalemia, symptomatic hypotension, and angioedema. There was no significant difference between the two trial groups in the incidence of any of these four adverse events. This information is of fundamental importance to clinicians who are deciding whether and how to initiate the use of sacubitril–valsartan in their patients with heart failure with reduced ejection fraction.

There are some limitations to the strength of the safety evidence in the trial. The confidence intervals for the relative risk of each safety outcome were quite wide and were consistent with increases of as much as 28% in worsening renal function, 84% in hyperkalemia, 64% in symptomatic hypotension, and 38% in angioedema with the use of sacubitril–valsartan. In addition, achievement of a safety profile similar to that seen in the PIONEER-HF trial would require reproduction of specific features of the PIONEER-HF trial design, including patient selection, timing of treatment, and drug dosing.

Nonetheless, the PIONEER-HF trial provides the best evidence available to guide the initiation of sacubitril–valsartan in patients with acute decompensated heart failure. One would anticipate that, if this treatment is initiated in-hospital as described in this report, and if the patient remains adherent to the treatment after hospital discharge, the long-term benefits on clinical outcomes that were seen in the PARADIGM-HF trial should be attainable. These findings may help to increase the adoption of this important addition to the heart-failure armamentarium.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

1. McMurray JJV, Packer M, Desai AS, et al. Angiotensin–neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993-1004.
2. Sangaralingham LR, Sangaralingham SJ, Shah ND, Yao X, Dunlay SM. Adoption of sacubitril/valsartan for the management of patients with heart failure. Circ Heart Fail 2018;11(2):e004302.
3. Yancy CW, Jessup M, Bozkurt B, et al. 2016 ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: an update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol 2016;68:1476-88.
4. Luo N, Ballew NG, O'Brien EC, et al. Early impact of guideline publication on angiotensin-receptor neprilysin inhibitor use among patients hospitalized for heart failure. Am Heart J 2018;200:134-40.
5. Lavoie KL, Rash JA, Campbell TS. Changing provider behavior in the context of chronic disease management: focus on clinical inertia. Annu Rev Pharmacol Toxicol 2017;57:263-83.
6. Manolis AS, Manolis TA, Manolis AA, Melita H. Neprilysin inhibitors: filling a gap in heart failure management, albeit amidst controversy and at a significant cost. Am J Cardiovasc Drugs 2018 June 20 (Epub ahead of print).
7. Gattis WA, O'Connor CM, Gallup DS, Hasselblad V, Gheorghiade M. Predischarge initiation of carvedilol in patients hospitalized for decompensated heart failure: results of the Initiation Management Predischarge: Process for Assessment of Carvedilol Therapy in Heart Failure (IMPACT-HF) trial. J Am Coll Cardiol 2004;43:1534-41.
8. Curtis LH, Mi X, Qualls LG, et al. Transitional adherence and persistence in the use of aldosterone antagonist therapy in patients with heart failure. Am Heart J 2013;165:979-986.e1.
9. Ambrosy AP, Mentz RJ, Fiuzat M, et al. The role of angiotensin receptor-neprilysin inhibitors in cardiovascular disease-existing evidence, knowledge gaps, and future directions. Eur J Heart Fail 2018;20:963-72.
10. Velazquez EJ, Morrow DA, DeVore AD, et al. Angiotensin–neprilysin inhibition in acute decompensated heart failure. N Engl J Med 2019;380:539-48.
11. Zile MR, Claggett BL, Prescott MF, et al. Prognostic implications of changes in N-terminal pro-B-type natriuretic peptide in patients with heart failure. J Am Coll Cardiol 2016;68:2425-36.

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