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Letter

TO THE EDITOR

Adoption of Sacubitril/Valsartan Must Take Into Account Different Heart Failure Patient Types

We read with great interest the paper by Luo et al. (1) about early adoption of sacubitril/valsartan (angiotensin II receptor blocker neprilysin inhibitor [ARNI]) therapy for patients with heart failure and reduced ejection fraction (HFrEF) from the GWTG-HF (Get With the Guidelines-Heart Failure) registry.

The authors observed that only 2.3% of patients discharged alive from hospitals in the large GWTG-HF registry were prescribed ARNI therapy in the first 12 months following U.S. Food and Drug Agency approval and considered this evidence a confirmed barrier to successful implementation of evidence-based medicine in clinical practice.

We are not surprised by these results, principally because the study population included only patients discharged after acute HF hospitalization.

By definition, this population is an unstable cohort and does not meet the criteria that were established in PARADIGM-HF (Prospective Comparison of ARNI with ACEI [angiotensin-converting-enzyme inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial) (2), which analyzed only outpatients who were receiving optimal medical therapy and were in a stable chronic HF condition. Seventy percent of the study population was in New York Heart Association functional class II, and patients who were hospitalized within 3 months previously to screening accounted for only 19% of the cohort.

Hospitalized patients are a heterogeneous and intensively treated subset, thus patients who are initiated on sacubitril/valsartan therapy during hospitalization may be unable to tolerate continuation of the medication on discharge. Starting a patient during hospitalization for acute HF has never yet been studied. Therefore, the main obstacle to more widespread initiation of ARNI in HFrEF patients during acute HF hospitalization may be the lack of compelling evidence supporting that practice. A preliminary observation in a small sample study (3) reported that only 44% of patients who had received ARNI during their admission were discharged on this therapy. The most common reason for medication discontinuation was hypotension. Studies of outcomes for HFrEF patients started on ARNI during hospitalization are needed and are incoming.

Therefore, it would be interesting to know how many patients had started receiving the drug, the rate of patients who were unable to tolerate the medication at discharge, the most common reason for drug discontinuation, and the clinical differences between patients who continued the drug and those who discontinued it.

Today's guidelines (4,5) recommend ARNI therapy only in chronic outpatients who remain symptomatic despite optimal treatment with an ACEI, a beta-blocker, and a mineralocorticoid-receptor antagonist. Therefore, the low rate of prescription observed by Luo et al. (1) may not translate *tout-court* (i.e., without elaboration) the real attitudes of the cardiologists to the implementation of this new therapy.

It is also our belief that there is a deleterious delay in the integration of new evidence into clinical practice; however, in this case the conclusion by the authors may not be completely adequate to confirm this assumption.

New data from large and structured surveys and registries of acute and chronic HF patients can provide additional elements to help us close the gap between evidence and real-world experience.

***Giuseppe Di Tano, MD**
Luca Bettari, MD
*Cardiology Department
Azienda Socio Sanitaria Territoriale, Cremona
Largo Priori 1
26100 Cremona
Italy
E-mail: giditano@tin.it

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REPLY: Adoption of Sacubitril/Valsartan Must Take Into Account Different Heart Failure Patient Types

We appreciate the interest by Drs. Di Tano and Bettari in our recent publication (1). We thank the authors for highlighting that our report included patients discharged after an acute heart failure (HF) hospitalization, a population different from those studied in the PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial (2). Drs. Di Tano and Bettari raise important questions regarding the differing characteristics of patients who initiate sacubitril/valsartan (ARNI) therapy during a hospitalization for HF and tolerate therapy through discharge versus those who discontinue therapy. Unfortunately, granular details around in-hospital medication adjustments and tolerability are not available as part of the Get With The Guidelines-HF registry.

Overall, we agree that patients hospitalized for acute HF are phenotypically different from those with ambulatory or chronic HF and deserve special attention regarding the initiation of novel therapies, such as ARNI. In this regard, ongoing clinical trials, such as TRANSITION (Comparison of Pre- and Post-discharge Initiation of LCZ696 Therapy in HFrEF Patients After an Acute Decompensation Event; NCT02661217) and PIONEER-HF (Comparison Of Sacubitril/valsartan Versus Enalapril on Effect on NTpro-BNP in Patients Stabilized From an Acute Heart Failure Episode; NCT02554890), will provide valuable information about safety and tolerability in this population.

Nevertheless, there remain additional questions that may not be answered through traditional clinical trials. As new therapies are adopted into clinical practice, real-world evidence supports better understanding of reasons for medication discontinuation (e.g., symptomatic hypotension, renal dysfunction, hyperkalemia) and the patient- and system-level barriers to use and uptake (e.g., out-of-pocket costs, formulary challenges). In this setting, proponents of early adoption are contrasted against those with more conservative perspectives. For instance, some clinician scientists have advocated for the systematic and timely implementation of ARNI therapy to improve patient outcomes given the potential magnitude of mortality benefit at the population level (3,4). Other groups including the American Academy of Family Physicians have endorsed a more cautious approach while data on potential harm accumulate (5). Novel initiatives, such as the National Patient-Centered Clinical Research Network (PCORnet), where a learning health care system embeds research within clinical care, can promote both goals simultaneously. Acquiring real-world patient tolerability data (including causes for discontinuation and practical dose titration) from population-based observational analyses is critically necessary, but this process need not delay the potential benefit afforded to appropriate patients with HF. Integrating emerging data from diverse settings will best support the understanding of how novel therapies affect patient-prioritized outcomes.

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

*Duke Clinical Research Institute
Room 0311 Terrace Level
2400 Pratt Street
Durham, North Carolina 27705
E-mail: emily.obrien@duke.edu

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