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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.

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