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EDITORIAL

Sacubitril–Valsartan in Heart Failure: Why Are More Physicians Not Prescribing It?

What if you were a patient with heart failure with reduced ejection fraction and your physician did not prescribe sacubitril–valsartan, a new drug that could prolong your life? Clinical trial data supported the drug's effectiveness, the U.S. Food and Drug Administration (FDA) expedited its approval, and U.S. guidelines recommended its use. Yet, you were stable while using several heart failure drugs, and the physician who saw you every 3 to 6 months never mentioned a newer medication, despite clinical trial data demonstrating mortality benefits of the drug in patients like you. You died suddenly one morning. Did your physician do anything wrong?

Sandhu and colleagues' article (1) is one of nearly 200 articles (and 3 cost-effectiveness analyses [1–3]) published in the past 3 years that support the benefits of sacubitril–valsartan in the treatment of heart failure. All have reported concordant, favorable results associated with switching patients from conventional renin–angiotensin inhibitors to sacubitril–valsartan. Sandhu and colleagues evaluated the cost-effectiveness of sacubitril–valsartan compared with lisinopril or losartan in 64-year-old patients with New York Heart Association (NYHA) class II to IV heart failure and left ventricular ejection fraction of 0.40 or less. They found that patients receiving sacubitril–valsartan experienced 0.69 additional life-year, 0.62 additional quality-adjusted life-year (QALY), and $29 203 in incremental costs, equating to a cost per QALY gained of $47 053. Of note, lisinopril and losartan, the least expensive members of their respective drug classes, were used as comparators, and neither drug (in contrast with enalapril) has been shown to reduce mortality in patients with heart failure. The authors concluded, as did the 2 previous cost-effectiveness analyses, that treatment with sacubitril–valsartan is cost-effective in reducing cardiovascular mortality and morbidity of chronic heart failure in patients with NYHA class II to IV heart failure.

Will this latest analysis persuade physicians not currently prescribing the drug to start doing so? We doubt it. A lack of convincing data is not the issue with sacubitril–valsartan; the evidence is compelling. Perhaps concern about cost has been an issue for some, but the cost-effectiveness analyses indicate that the drug provides excellent value. Safety is not the issue; in clinical trials, patients with heart failure tolerated the drug better than conventional inhibitors of the renin–angiotensin system (4). So how can we persuade physicians to prescribe sacubitril–valsartan?

Three of the authors (W.M.A., J.M.R., and M.E.) have never prescribed sacubitril–valsartan, even though 2 (W.M.A. and J.M.R.) are busy internists. One author (M.P.) was 1 of the 2 principal investigators of the PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial, which demonstrated a survival advantage of sacubitril–valsartan and formed the basis for the approval by the FDA and its favorable recommendation in current guidelines (5). The 4 of us discussed the slow uptake of this new drug and ways of persuading physicians to prescribe it. This editorial summarizes our collective thoughts.

Physicians are persuaded by knowledge and evidence. So what do we know about sacubitril–valsartan? It inhibits both the renin–angiotensin system and neprilysin and reverses hemodynamic, neurohormonal, and renal abnormalities in heart failure more effectively than an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin-receptor blocker (6, 7). Clinically stable patients with only mild heart failure symptoms on a conventional renin–angiotensin system inhibitor have been shown to benefit more from switching to sacubitril–valsartan than patients with more severe symptoms (1, 7, 8). The most common mode of death in patients with clinically stable heart failure and mild symptoms is sudden cardiac death; patients who seem well are at high risk for dying suddenly without any preceding worsening of symptoms. In the PARADIGM-HF trial, switching patients from an ACE inhibitor or an angiotensin-receptor blocker to sacubitril–valsartan reduced the risk for sudden cardiac death (6.0% vs. 7.4%; hazard ratio, 0.80 [95% CI, 0.68 to 0.94]), even in patients receiving other treatments that reduce the risk for sudden death, such as β-blockers and implantable cardioverter-defibrillators (9). The superiority of sacubitril–valsartan over conventional renin–angiotensin inhibitors is apparent within 30 days of starting treatment with the angiotensin receptor–neprilysin inhibitor (6).

The survival benefits of switching patients to sacubitril–valsartan are substantial. The PARADIGM-HF trial found an incremental 20% reduction in cardiovascular death beyond that achieved with enalapril (6, 7). This finding may not be persuasive if physicians believe that their patients are not at significant risk for death. However, physicians should recognize that patients with mild to moderate heart failure are at greater risk for dying than many patients with cancer (7, 9). Using patient-level data, the PARADIGM-HF investigators estimated that treatment with sacubitril–valsartan prolongs life by an average of 1.0 to 2.0 years (10). The difference in this estimate from that of Sandhu and colleagues (6 to 7 months) is that the actual trial data demonstrated a relatively "flat" age-versus-risk relationship, because patients who develop heart failure at a young age tend to have more severe heart failure than those who develop it at an older age. In the absence of patient-level data, Sandhu and colleagues assumed that the age–risk gradient for patients with heart failure

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mirrors that of the general population, when in fact the PARADIGM-HF data suggest otherwise. If they had used patient-level estimates in their calculations, the cost-effectiveness of sacubitril–valsartan would have been even more favorable than they reported.

We believe that, when they consider these findings, physicians who previously never prescribed sacubitril–valsartan would take the drug themselves if they had heart failure—even if they were clinically stable and had minimal symptoms. Yet, the plethora of articles and *P* values concerning sacubitril–valsartan published over the past 3 years have had minimal impact on prescribing behaviors.

This experience has important lessons for those who believe that publishing numerous articles will meaningfully influence clinical practice. Many physicians are too busy caring for patients to spend time reading research reports on new and unfamiliar drugs. Furthermore, even if physicians were to read the findings of a new study, they are likely to encounter data that are presented in an opaque and unpersuasive manner. For many, publications are simply a way that researchers talk to each other rather than communicating with physicians who are responsible for the care of most patients. This is a lesson the academic clinical community needs to hear and take to heart.

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