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Heart Failure Guideline-Directed Medical Therapy in End-Stage Kidney Disease: From PARADIGM-HF to Clinical Practice

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The management of heart failure (HF) in patients with end-stage kidney disease (ESKD) presents unique challenges, compounded by uncertainties in applying guideline-directed medical therapies, which have shown significant benefits in the broader population with HF. Historically, pivotal HF trials have excluded patients with advanced kidney dysfunction. This exclusion has led to a notable gap in clinical knowledge, directly impacting current guidelines, which consequently offer limited recommendations for the management of HF in patients requiring dialysis. Reflecting this gap, real-world data from a registry analysis of over 300,000 HF hospitalizations indicates a lower utilization of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and mineralocorticoid receptor antagonists among patients with ESKD.[1] Notably, in the same report, 38% of patients requiring dialysis received either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers at the time of discharge, but only 2% were prescribed sacubitril/valsartan.

In this issue of Kidney International Reports, the study by Charkviani *et al.*[2] emerges as a commendable attempt to explore the role of sacubitril/valsartan beyond the well-charted territories defined by the landmark PARADIGM-HF and PARAGON-HF trials.[3,4] These foundational studies have positioned sacubitril/valsartan as a cornerstone in the management of HF. In PARADIGM-HF, sacubitril/valsartan markedly improved outcomes compared to enalapril in patients with HF and reduced ejection fraction.[3] In PARAGON-HF, which enrolled patients with HF and preserved ejection fraction, sacubitril/valsartan narrowly missed statistical significance for its primary end point.[4] However, a subgroup analysis suggested potential benefits in subjects with below-normal left ventricular ejection fraction. This finding was instrumental in the decision by the US Food and Drug Administration to broaden the approved indications of sacubitril/valsartan to patients with HF and preserved ejection fraction.

Hyperkalemia, a common side effect of most HF guideline-directed medical therapies, is of particular relevance in patients with ESKD. A secondary analysis of PARADIGM-HF suggested that sacubitril/valsartan may result in a lower incidence of this condition.[5] Conversely, the LIFE Study,[6] a trial which investigated the use of this drug in patients with advanced HF and an estimated glomerular filtration rate >20 ml/min per 1.73 m^2, showed an increased risk for hyperkalemia with sacubitril/valsartan compared to valsartan. These contrasting findings underscore the complexity of translating HF treatments to populations, which differ from the ones studied in the original investigations, and further highlights the challenges of applying existing evidence to the management of patients with ESKD.

From the analysis of Charkviani *et al.*,[2] the lack of safety data in the literature clearly emerges as a major limitation preventing a more widespread use of sacubitril/valsartan in ESKD. Of the 12 included studies, only 3 compared the rates of hyperkalemia between sacubitril-valsartan and a control group, and only 2 addressed hypotension. However, the work of Charkviani *et al.*[2] also suggests

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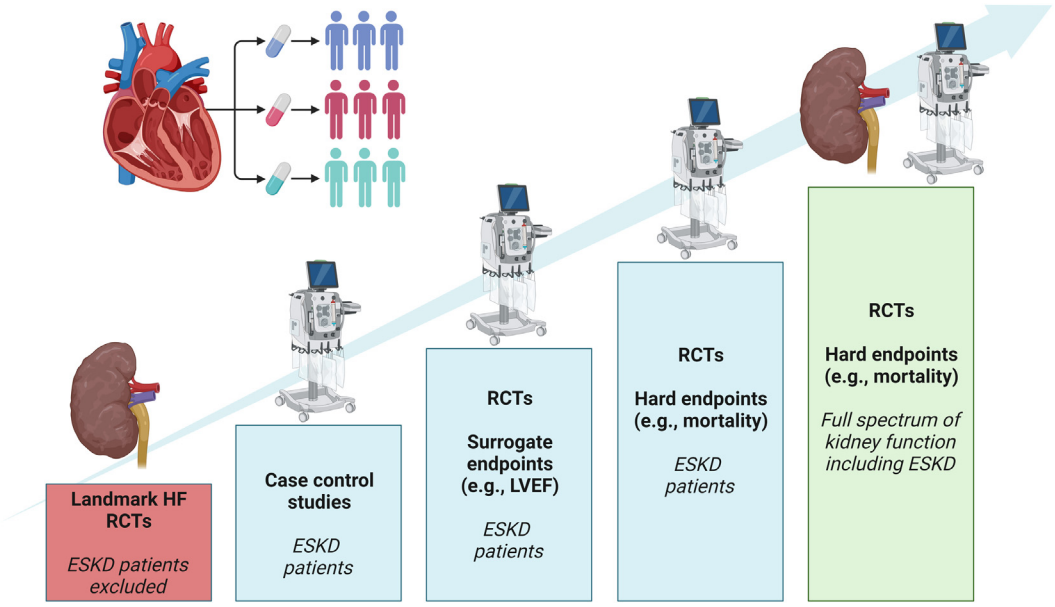

Figure 1. Heart failure guideline-directed medical therapy in end-stage kidney disease: advancing the evidence. This figure presents a potential pathway, tracing the trajectory from landmark studies that have excluded patients with end-stage kidney disease to future randomized controlled trials designed to enroll subjects across the full spectrum of kidney function. ESKD, end-stage kidney disease; HF, heart failure; RCTs, randomized controlled trials.

that sacubitril/valsartan may result in an improvement of left ventricular ejection fraction in patients with impaired systolic function, in line with the evidence available in the broader population with HF.

The prospect of clinical trials that could conclusively demonstrate the impact of sacubitril/valsartan and other guideline-directed medical therapy agents on hard end points in ESKD is fraught with challenges. Given the multifactorial nature of adverse outcomes in this population—where HF is a significant, yet not isolated contributor—a trial powered on cardiovascular mortality would require a prohibitively large sample size to detect meaningful differences. It remains to be determined whether to evaluate the efficacy and safety of HF medications within ESKD-specific trials or through broader studies that encompass the full spectrum of kidney function (Figure 1). Pending definitive evidence, smaller randomized studies focusing on safety and surrogate markers may offer valuable insights. Building upon the work of Charkviani *et al.*[2] and the insights from PARADIGM-HF and PARAGON-HF, future studies on sacubitril/valsartan should enroll primarily patients with reduced ejection fraction, targeting measurable improvements in systolic function and monitoring key safety indicators such as hyperkalemia and hypotension.

In conclusion, the study by Charkviani *et al.*[2] offers a meaningful addition to the ongoing debate regarding HF management within the context of ESKD. For the cardiology and nephrology communities, the objective remains to substantiate the initial findings of this meta-analysis with larger trials that could eventually provide more definitive guidance on the use of sacubitril/valsartan and other HF therapies in ESKD. The integration of such evidence into clinical practice has the potential to significantly improve outcomes and enhance the quality of life of patients burdened by the dual challenges of HF and kidney disease.

DISCLOSURE

All the authors declared no competing interests.

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