JACC: HEART FAILURE VOL. ■, NO. ■, 2018

Renal Effects and Associated Outcomes During Angiotensin-Neprilysin Inhibition in Heart Failure

Kevin Damman, MD, PhD,[a] Mauro Gori, MD,[b,c] Brian Claggett, PhD,[b] Pardeep S. Jhund, MB, PhD,[d] Michele Senni, MD,[c] Martin P. Lefkowitz, MD,[e] Margaret F. Prescott, PhD,[e] Victor C. Shi, MD,[e] Jean L. Rouleau, MD,[f] Karl Swedberg, MD, PhD,[g,h] Michael R. Zile, MD,[i] Milton Packer, MD,[j] Akshay S. Desai, MD, MPH,[b] Scott D. Solomon, MD,[b] John J.V. McMurray, MD[d]

ABSTRACT

OBJECTIVES The purpose of this study was to evaluate the renal effects of sacubitril/valsartan in patients with heart failure and reduced ejection fraction.

BACKGROUND Renal function is frequently impaired in patients with heart failure with reduced ejection fraction and may deteriorate further after blockade of the renin–angiotensin system.

METHODS In the PARADIGM-HF (Prospective Comparison of ARNI with ACE inhibition to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial, 8,399 patients with heart failure with reduced ejection fraction were randomized to treatment with sacubitril/valsartan or enalapril. The estimated glomerular filtration rate (eGFR) was available for all patients, and the urinary albumin/creatinine ratio (UACR) was available in 1872 patients, at screening, randomization, and at fixed time intervals during follow-up. We evaluated the effect of study treatment on change in eGFR and UACR, and on renal and cardiovascular outcomes, according to eGFR and UACR.

RESULTS At screening, the eGFR was 70 ± 20 ml/min/1.73 m^2 and 2,745 patients (33%) had chronic kidney disease; the median UACR was 1.0 mg/mmol (interquartile range: 0.4 to 3.2 mg/mmol) and 24% had an increased UACR. The decrease in eGFR during follow-up was less with sacubitril/valsartan compared with enalapril (−1.61 ml/min/1.73 m^2/year; [95% confidence interval: −1.77 to −1.44 ml/min/1.73 m^2/year] vs. −2.04 ml/min/1.73 m^2/year [95% CI: −2.21 to −1.88 ml/min/1.73 m^2/year]; $p < 0.001$) despite a greater increase in UACR with sacubitril/valsartan than with enalapril (1.20 mg/mmol [95% CI: 1.04 to 1.36 mg/mmol] vs. 0.90 mg/mmol [95% CI: 0.77 to 1.03 mg/mmol]; $p < 0.001$). The effect of sacubitril/valsartan on cardiovascular death or heart failure hospitalization was not modified by eGFR, UACR (p interaction = 0.70 and 0.34, respectively), or by change in UACR (p interaction = 0.38).

CONCLUSIONS Compared with enalapril, sacubitril/valsartan led to a slower rate of decrease in the eGFR and improved cardiovascular outcomes, even in patients with chronic kidney disease, despite causing a modest increase in UACR.
(J Am Coll Cardiol HF 2018;■:■–■) © 2018 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Department of Cardiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; [b]Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, Massachusetts; [c]Cardiovascular Department, Azienda Ospedaliera Papa Giovanni XXIII Hospital, Bergamo, Italy; [d]British Heart Foundation (BHF) Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom; [e]Novartis Pharmaceuticals, East Hanover, New Jersey; [f]Institut de Cardiologie de Montréal, Université de Montréal, Montreal, France; [g]Department of Molecular and Clinical Medicine, University of Gothenburg, Gothenburg, Sweden; [h]National Heart and Lung Institute, Imperial College London, London, United Kingdom; [i]Medical University of South Carolina and Ralph H. Johnson Veterans Affairs Medical Center, Charleston, South Carolina; and the [j]Baylor Heart and Vascular Institute, Baylor University Medical Center, Dallas, Texas. The PARADIGM HF study was funded by Novartis. Dr. Claggert is a consultant for Gilead, AO Biome, and Boehringer Ingelheim. Dr. Jhund is a consultant for and has received speaker and advisory board fees from Novartis. Drs. Lefkowitz, Prescott, and Shi are employees of and own stock in Novartis Pharmaceuticals. Dr. Rouleau is a consultant for Novartis, Bayer, and AstraZeneca. Drs. Swedberg and Zile are consultants for Novartis. Dr. Packer is a consultant for Amgen, AstraZeneca, Bayer Boehringer Ingelheim, Cardiorentis, Saiichi Sankyo, Gilead, NovoNordisk, Novartis, Relypsa, Sanofi, Teva, Takeda, and ZS Pharma. Dr. Desai has received consulting fees and research support from Novartis. Dr. Solomon has received research grants from and is a consultant for Novartis. Dr. McMurray is an employee of Glasgow University, and Glasgow University has been paid by Novartis for his participation in a number of trials,

ISSN 2213-1779 https://doi.org/10.1016/j.jchf.2018.02.004

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

CKD = chronic kidney disease

eGFR = estimated glomerular filtration rate

HFrEF = heart failure with reduced ejection fraction

HR = hazard ratio

RAAS = renin-angiotensin-aldosterone system

IQR = interquartile range

UACR = urinary albumin/creatinine ratio

Renin-angiotensin-aldosterone system (RAAS) inhibition is the cornerstone of treatment of patients with heart failure with reduced ejection fraction (HFrEF) (1). Furthermore, in patients without diabetes and nephropathy, RAAS inhibition reduces urinary albumin excretion and slows progression to end-stage renal disease (2,3). However, the use of RAAS inhibitors may be limited by an increase in serum creatinine, often resulting in treatment discontinuation (1). This move is especially disadvantageous in HFrEF patients with chronic kidney disease (CKD) who are at particularly high risk of adverse outcomes, and have the greatest absolute risk reduction with RAAS inhibition (4).

Recently, the combined angiotensin receptor-neprilysin inhibitor, sacubitril/valsartan (formerly known as LCZ696), was shown to reduce the risk of death and hospital admission, compared with enalapril, in patients with HFrEF (5). However, sacubitril/valsartan did not reduce the pre-specified composite renal endpoint of a decrease in the estimated glomerular filtration rate (eGFR) of ≥50%, or by >30 ml/min/1.73 m^2 from baseline (and to <60 ml/min/1.73 m^2), or progression to end-stage renal disease. Moreover, sacubitril/valsartan is known to increase the urinary albumin/creatinine ratio (UACR) in patients with heart failure and preserved ejection fraction (6). Given the importance of kidney function in patients with HFrEF, and the potential interactions between eGFR, UACR, and the effect of therapy in HFrEF, we conducted a comprehensive analysis of the PARADIGM-HF (Prospective Comparison of ARNI with ACE inhibition to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial. We describe the effects of sacubitril/valsartan and enalapril on eGFR and UACR and the relationship between changes in eGFR and UACR and cardiovascular and renal outcomes, according to treatment assignment (5,7).

METHODS

The design and results of PARADIGM-HF have been reported elsewhere (5,7). The trial received local ethics committee approval and all patients gave written, informed consent. Briefly, patients in New York Heart Association functional classes II to IV with an ejection fraction of ≤40%, and elevated levels of plasma B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide were enrolled. Patients were required to be treated with an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker in a dose equivalent to at least enalapril 10 mg/day for at least 4 weeks before screening, along with a stable dose of beta-blocker (unless contraindicated or not tolerated) and a mineralocorticoid receptor antagonist (if indicated). Exclusion criteria included symptomatic hypotension (or a systolic blood pressure <100 mm Hg at screening or <95 mm Hg at random treatment assignment), an eGFR of <30 ml/min/1.73 m^2 at screening or random treatment assignment (or a decrease >25% [amended to >35%] between screening and random treatment assignment), and hyperkalemia (serum potassium >5.2 mmol/l at screening or >5.4 mmol/l at random treatment assignment).

On trial entry, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker treatment was discontinued, and patients entered sequential single-blind run in phases (enalapril for 2 weeks, followed by sacubitril/valsartan for 4 to 6 weeks, with uptitration). Patients tolerating both drugs were then randomly assigned to double-blind treatment in a 1:1 ratio with either enalapril 10 mg or sacubitril/valsartan 97/103 mg twice daily.

ESTIMATION OF eGFR AND UACR. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (8) with creatinine traceable to isotope dilution mass spectrometry. The glomerular filtration rate was estimated at screening, random treatment assignment, at 2, 4, and 8 weeks, and 4 months after random treatment assignment; and every 4 months thereafter. By protocol, in a subset of patients, urinary albumin and creatinine concentrations, measured in spot urine samples (transferred at ambient temperature to a central laboratory for immediate analysis), were used to calculate the UACR. Urinary albumin was analyzed using the Roche Tina-quant chemiluminescent immunoassay. The UACR was determined at screening, random treatment assignment, and at 1 and 8 months after random treatment assignment. Normoalbuminuria was defined as a UACR of <3.5 mg/mmol, microalbuminuria

including PARADIGM-HF and lectures, advisory boards, and other meetings related to PARADIGM-HF and sacubitril/valsartan. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Damman and Gori contributed equally to this work and are joint first authors. Drs. Solomon and McMurray contributed equally to this work and are joint senior authors.

Manuscript received January 23, 2018; accepted February 7, 2018.