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Worsening Renal Function and Outcome in Heart Failure Patients With Preserved Ejection Fraction and the Impact of Angiotensin Receptor Blocker Treatment

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ABSTRACT

BACKGROUND Worsening renal function (WRF) associated with renin-angiotensin-aldosterone system (RAAS) inhibition does not confer excess risk in heart failure patients with reduced ejection fraction (HFrEF).

OBJECTIVES The goal of this study was to investigate the relationship between WRF and outcomes in heart failure patients with preserved ejection fraction (HFpEF) and the interaction with RAAS blockade.

METHODS In 3,595 patients included in the I-PRESERVE (Irbesartan in Heart Failure With Preserved Ejection Fraction) trial, change in estimated glomerular filtration rate (eGFR) and development of WRF after initiation of irbesartan or placebo were examined. We examined the association between WRF and the first occurrence of cardiovascular death or heart failure hospitalization (primary outcome in this analysis) and the interaction with randomized treatment.

RESULTS Estimated GFR decreased early with irbesartan treatment and remained significantly lower than in the placebo group. WRF developed in 229 (6.4%) patients and occurred more frequently with irbesartan treatment (8% vs. 4%). Overall, WRF was associated with an increased risk of the primary outcome (adjusted hazard ratio [HR]: 1.43; 95% confidence interval [CI]: 1.10 to 1.85; $p = 0.008$). Although the risk related to WRF was greater in the irbesartan group (HR: 1.66; 95% CI: 1.21 to 2.28; $p = 0.002$) than with placebo (HR: 1.09; 95% CI: 0.66 to 1.79; $p = 0.73$), the interaction between treatment and WRF on outcome was not significant in an adjusted analysis.

CONCLUSIONS The incidence of WRF in HFpEF was similar to that previously reported in HFrEF but more frequent with irbesartan than with placebo. WRF after initiation of irbesartan treatment in HFpEF was associated with excess risk, in contrast to WRF occurring with RAAS blockade in HFrEF. (J Am Coll Cardiol 2014;64:1106–13) © 2014 by the American College of Cardiology Foundation.

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Deterioration of renal function over time, termed worsening renal function (WRF), is associated with worse outcomes in patients with acute and chronic heart failure (HF) (1). Although this association has been established in patients with HF with reduced ejection fraction (HFrEF), no data exist regarding the relationship between WRF and outcomes in HF patients with preserved ejection fraction (HFpEF). Furthermore, controversy persists about whether WRF is always associated with poor outcome. Recent studies suggest that the cause of renal function decline, the circumstances under which it occurs, and the concomitant therapy used may be far more important than the actual occurrence of WRF itself (2–4). Notably, WRF after initiation of renin-angiotensin-aldosterone system (RAAS) inhibitors in clinical trials has not been associated with poor outcome, but WRF is prognostic when it occurs in the placebo group (5–8). Furthermore, the benefit associated with RAAS blockade was observed in both patients with and without WRF, implying that WRF does not alter the benefit of therapy.

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In the present study, we investigated change in estimated glomerular filtration rate (eGFR) over time, the occurrence of WRF and its association with clinical outcomes, and interaction with randomized treatment in patients with HFpEF included in the I-PRESERVE (Irbesartan in Heart Failure With Preserved Ejection Fraction) trial.

PATIENTS AND METHODS

The design and results of I-PRESERVE have been published previously (9). In brief, 4,128 patients ≥60 years of age, with signs and symptoms of HF and a preserved left ventricular ejection fraction (≥45%) were randomized to receive placebo or irbesartan 300 mg once daily. Patients were started on 75 mg of irbesartan or placebo once daily. The dose was doubled to 150 mg after 1 to 2 weeks and doubled again to 300 mg after an additional 1 to 2 weeks, as tolerated. Patients with a baseline serum creatinine (SCr) level >221 μmol/l (2.5 mg/dl) were excluded from the study. Patients with an SCr measurement at baseline and at the visit 8 weeks after randomization were included in the present analysis.

GFR AND WRF. The eGFR was calculated by using the simplified Modification of Diet in Renal Disease formula at baseline and subsequent visits (2 and 8 weeks and 6, 18, and 30 months). WRF was defined as an absolute increase in SCr of ≥26.5 μmol/l (≥0.3 mg/dl), together with a relative increase in SCr of ≥25% between baseline and 8 weeks (the period during which forced titration of randomized treatment occurred). In addition, as sensitivity analyses, we also calculated WRF defined as an absolute increase in SCr ≥26.5 μmol/l or a reduction in eGFR ≥20%, all at 8 weeks. Finally, we assessed early WRF 2 weeks after randomization for each definition.

OUTCOMES. For the present analysis, the primary outcome was the first occurrence of cardiovascular death or HF hospitalization. Secondary outcomes included all-cause mortality, HF hospitalization, the combined endpoint of all-cause mortality or HF hospitalization, and the primary endpoint of the I-PRESERVE trial, which was the composite of all-cause mortality or first hospitalization for a protocol-specified adjudicated cardiovascular hospitalization (defined as worsening HF, unstable angina, myocardial infarction, ventricular arrhythmia, atrial arrhythmia, or stroke). All outcomes were adjudicated by an independent clinical endpoint committee.

STATISTICAL ANALYSIS. Data are reported as mean ± SD when normally distributed, as median and interquartile ranges when the distribution was skewed, and as frequencies and percentages for categorical variables. The Student *t* test or Mann-Whitney *U* tests were used to determine significant differences in variables between patients with and without WRF in both treatment groups. Logistic regression was used to determine odds ratios for the occurrence of WRF at 8 weeks. Change in renal function over time was assessed by using repeated analysis mixed-effect modeling. Multivariable modeling was adjusted for variables previously shown to be of prognostic value in this population (10).

Covariates adjusted for as fixed effects were: age; sex; race; etiology of HF; New York Heart Association functional class; left ventricular ejection fraction; systolic and diastolic blood pressures; heart rate; history of myocardial infarction, hypertension, atrial fibrillation, stroke, and diabetes; baseline medical therapy (angiotensin-converting enzyme inhibitor, beta-blocker, diuretics, digoxin, and spironolactone); and measurement of N-terminal pro-B-type natriuretic peptide (NT-proBNP, logarithmically transformed). Patients were included as random effects, and time was modeled linearly. A Cox proportional hazards model was used to estimate hazard ratios with 95% confidence intervals for the occurrence of the primary and all secondary endpoints. WRF was

ABBREVIATIONS AND ACRONYMS

eGFR = estimated glomerular filtration rate

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

MAP = mean arterial blood pressure

MRA = mineralocorticoid receptor antagonist

NT-proBNP = N-terminal pro-B-type natriuretic peptide

RAAS = renin-angiotensin-aldosterone system

SCr = serum creatinine

WRF = worsening renal function