JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER INC.

VOL. 64, NO. 11, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2014.01.087

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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Manuscript received November 29, 2013; revised manuscript received January 21, 2014, accepted January 28, 2014.

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

entered into the model as a categorical variable. Interaction terms with treatment (WRF × treatment) were analyzed for each definition of WRF separately. Kaplan-Meier survival curves were plotted showing outcomes in patients who did or did not experience WRF in both treatment groups. A 2-tailed p value <0.05 was considered significant, except for interactions in which p < 0.10 was considered significant. We chose a liberal cutoff point for the p value of significant interactions to allow better discrimination between false-negative and clinically significant interactions in light of the low event rates. Statistical analyses were performed by using Stata version 12.0 (Stata Corp., College Station, Texas).

RESULTS

A total of 3,595 patients (87% of all randomized patients) with an SCr measurement available at both baseline and 8 weeks formed the study population. Baseline characteristics are shown in **Table 1**. Compared with the entire I-PRESERVE study population, these patients had a slightly higher mean baseline SCr level but a similar eGFR, were more frequently male, and more often had ischemic heart disease, diabetes, and atrial fibrillation (data not shown).

CHANGE IN EGFR AND WRF. During the study, mean eGFR decreased from 73 ± 23 to 68 ± 21 ml/min/1.73 m^2 at 30 months. This finding translates into a change in eGFR of -2.2 ± 7.3 ml/min/1.73 m^2 per year. **Figure 1** displays the trends of eGFR over time in patients randomized to receive placebo or irbesartan. A significant difference between the 2 treatment groups persisted throughout the entire study period. The mean overall decrease in eGFR in the placebo group was -3.4 ± 23 ml/min/1.73 m^2 versus -7.2 ± 23 ml/min/1.73 m^2 in the irbesartan group (p < 0.001) at 30 months. Patients in the irbesartan group experienced a rapid, small initial decrease in eGFR; both groups

TABLE 1 Baseline Characteristics of Patients With and Without WRF

	Irbesartan			Placebo		
	WRF	No WRF	p Value	WRF	No WRF	p Value
Patients	153 (8)	1,659 (92)		76 (4)	1,707 (96)	
Age, yrs	73 ± 7	71 ± 7	0.06	72 ± 7	72 ± 7	0.42
Male	76 (50)	647 (39)	0.001	32 (42)	647 (38)	0.46
Heart rate, beats/min	73 ± 10	72 ± 11	0.17	73 ± 11	71 ± 10	0.02
SBP, mm Hg	138 ± 17	137 ± 15	0.60	137 ± 18	136 ± 15	0.36
DBP, mm Hg	79 ± 9	79 ± 9	0.87	80 ± 10	79 ± 9	0.36
BMI, kg/m^2	30 ± 6	30 ± 5	0.31	30 ± 7	29 ± 5	0.15
LVEF, %	58 ± 8	60 ± 9	0.02	59 ± 8	60 ± 9	0.55
Ischemic HF	39 (25)	427 (26)	0.46	11 (14)	407 (24)	0.37
Medical history						
Hypertension	86	90	0.14	89	88	0.74
Diabetes	34	26	0.038	38	26	0.024
Atrial fibrillation	37	28	0.026	29	29	0.94
Stroke	10	9	0.64	4	9	0.10
Myocardial infarction	27	23	0.25	18	23	0.36
Laboratory						
Hemoglobin, g/dl	13.9 ± 1.5	14.0 ± 1.5	0.40	13.8 ± 1.6	14.0 ± 1.5	0.19
Creatinine, μmol/l*	92 ± 30	88 ± 28	0.11	84 ± 26	88 ± 28	0.19
eGFR, ml/min/1.73 m^2	74 ± 29	73 ± 21	0.60	78 ± 27	73 ± 23	0.03
NT-proBNP, pg/ml	1,163 (177–1,238)	854 (136–942)	0.019	843 (138–992)	786 (128–928)	0.98
Medical therapy						
ACE inhibitors	29	25	0.29	25	24	0.80
MRAs	27	14	<0.001	24	14	0.026
Loop diuretics*	70	51	<0.001	53	52	0.91
Beta-blockers	61	60	0.77	53	59	0.29
NSAIDs	7	8	0.66	12	8	0.30
Digoxin	16	14	0.33	16	13	0.46

Values are n (%), mean ± SD, %, or median (interquartile range). *Significant interaction between WRF and treatment allocation.

ACE = angiotensin-converting enzyme; BMI = body mass index; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HF = heart failure; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NSAIDs = nonsteroidal anti-inflammatory drugs; NT-proBNP = N-terminal pro–B-type natriuretic peptide; SBP = systolic blood pressure; WRF = worsening renal function.

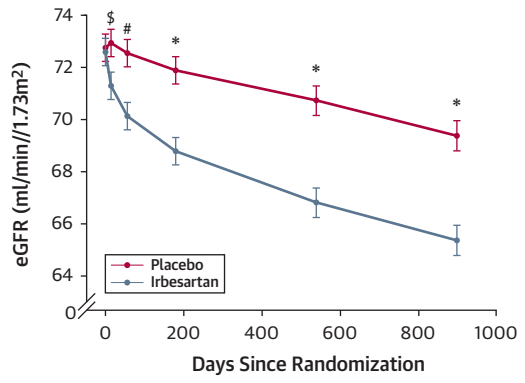


FIGURE 1 Change in eGFR Over Time Stratified According to Randomized Treatment Allocation

Presented are least squares means ± SEs from adjusted mixed-effects repeated measurements model. Patients were considered a random effect and the following were fixed effects: age; sex; race; etiology of heart failure; 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, or diabetes; baseline medical therapy (angiotensin-converting enzyme inhibitor, beta-blocker, diuretics, digoxin, and spironolactone use); and N-terminal pro-B-type natriuretic peptide measurement. $p < 0.050, #p < 0.01, *p < 0.001. For overall interaction, p <0.001. eGFR = estimated glomerular filtration rate.

demonstrated a similar slower decrease in eGFR over time (p for interaction time and allocated treatment <0.001).

WRF at 8 weeks developed in 229 (6.4%) patients. Patients randomized to irbesartan treatment experienced WRF more often (8.4% vs. 4.3%; odds ratio: 2.07; 95% confidence interval: 1.56 to 2.75; p < 0.001). The incidence of WRF according to the other prespecified definitions is presented in Online Table 1. WRF at 2 weeks was less frequent compared with the occurrence at 8 weeks. Clinical characteristics of patients with WRF according to treatment allocation are presented in **Table 1**. In general, there were few differences between patients with and without WRF; the main differences were presence of diabetes, higher NT-proBNP concentrations, use of diuretics, and treatment with a mineralocorticoid receptor antagonist (MRA). These differences were more pronounced in patients allocated to irbesartan treatment, although the only significant interaction between WRF and treatment allocation was seen for baseline SCr level and diuretic treatment.

Patients who experienced WRF at week 8 had similar discontinuation rates of randomized treatment at weeks 2 and 8. Overall, study drug discontinuation rates were very low, with no difference observed between the placebo and irbesartan groups. Occurrence of WRF was not associated with changes in either MRA or loop diuretic therapy. In the irbesartan group, patients developing WRF exhibited a significantly greater reduction in mean arterial blood pressure (MAP) at week 8 (-6.8 ± 11 mm Hg) compared with those who did not experience WRF (-4.0 ± 11 mm Hg; p = 0.003). In the placebo group, the reduction in MAP at week 8 was similar in those with and without WRF (-2.0 ± 12 mm Hg vs. -1.6 ± 11 mm Hg; p = 0.76). The decrease in MAP in patients developing WRF in the irbesartan group was significantly larger than the fall in MAP in those developing WRF in the placebo group (p = 0.003). In a mixed-effect linear model, changes in MAP showed a significant positive association with changes in eGFR over time, and there was a significant multivariate adjusted interaction between irbesartan treatment allocation, changes in MAP, and change in eGFR over time (p = 0.004).

WRF, IRBESARTAN TREATMENT, AND OUTCOME. During a mean follow-up of 46 months, the primary outcome (cardiovascular death or HF hospitalization) occurred in 895 patients. A total of 85 patients (37%) with WRF and 810 patients (24%) without WRF reached the combined endpoint. WRF was associated with an increased risk of developing the primary outcome (univariate hazard ratio: 1.75; 95% confidence interval: 1.41 to 2.17; p < 0.001). In the univariate analyses, WRF defined in the various prespecified methods was consistently related to a poor outcome, as documented in **Table 2** and Online Table 1.

However defined, WRF befalling patients allocated to irbesartan treatment was associated with more frequent occurrence of the primary outcome. The only exception was a decrease in eGFR at 2 weeks. Importantly, in the main analysis, treatment allocation interacted with the relationship between WRF and outcome: WRF exhibited a stronger relationship with outcome in the irbesartan group (**Central Illustration**). In multivariable analysis, WRF was associated with the primary outcome in the overall population and the irbesartan treatment group but not the placebo group (**Table 3**, Online Table 2). In addition, WRF was strongly associated with all secondary outcomes, with a similar magnitude of association (**Table 4**, Online Table 3). After multivariable adjustment, the interaction between treatment allocation and WRF on the effect of cardiovascular death or HF hospitalization was no longer significant, although it remained so for all-cause mortality,

TABLE 2 Univariate Analysis: WRF and Cardiovascular Death and HF Hospitalizations

	Overall Incidence (%)	OR for WRF With Irbesartan	p Value	Overall		Placebo		Irbesartan		p Value Interaction*
				HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	
≥0.3 mg/dl and ≥25% increase in creatinine	229 (6.4)	2.07 (1.56–2.75)	<0.001	1.75 (1.41–2.17)	<0.001	1.27 (0.85–1.93)	0.25	1.97 (1.50–2.58)	<0.001	0.084
≥0.3 mg/d increase in creatinine	245 (6.8)	2.13 (1.62–2.80)	<0.001	1.84 (1.49–2.26)	<0.001	1.32 (0.89–1.96)	0.17	2.10 (1.62–2.72)	<0.001	0.055
≥20% decrease in eGFR	412 (11.5)	1.82 (1.47–2.25)	<0.001	1.35 (1.12–1.62)	0.002	1.25 (0.92–1.69)	0.16	1.33 (1.04–1.70)	0.021	0.72

*Interaction between WRF and treatment on outcome. WRF defined at 8 weeks.
CI = confidence interval; HR = hazard ratio; OR = odds ratio; other abbreviations as in Table 1.

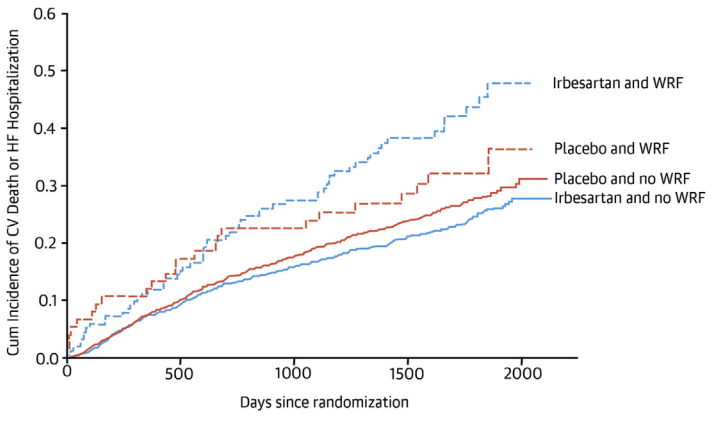
all-cause mortality or HF hospitalization, and the primary outcome of I-PRESERVE. No interactions occurred between either baseline NT-proBNP or diuretic use or MRA use, and the relationship between WRF, treatment, and outcome. WRF defined by changes up to 2 weeks were not independently associated with outcome, and none of the interaction terms between treatment and WRF was significant.

DISCUSSION

In the present study, we found that WRF occurred more frequently in patients allocated to treatment with irbesartan compared with placebo. Overall, the occurrence of WRF was associated with worse clinical outcomes compared with no WRF. This association seemed to be stronger in patients receiving irbesartan compared with placebo, contrasting strikingly with studies of RAAS inhibition in HFrEF (7,8,13).

WRF IN HFPEF AND HFREF. A large number of epidemiological studies in acute and chronic HF have shown an association between the development of WRF and poor clinical outcomes, including death (1,4–6,11–13). However, recent data from randomized clinical trials in HFrEF patients as well as studies in acute HF have questioned this association. In acute HF, WRF does not always portend a poor prognosis. In clinical trials, WRF was not associated with poor outcomes unless patients saw no decrease in systolic blood pressure or persistent congestion (2,4). Furthermore, although more intense diuretic treatment may lead to (transient) increases in SCr, such treatment is not associated with excess mortality (14). These observations suggest that it is not the development of WRF per se that is important but the circumstances under which it develops (or what causes it).

The present study differs from earlier observations because we investigated a chronic HFpEF population, which, to our knowledge, has not been studied before. One study did, however, investigate WRF developing in HFpEF patients admitted for HF. In that study, Rusinaru et al. (15) found that in-hospital WRF was predictive of 7-year outcome but only in patients with a reduced eGFR at baseline. To date, no substudy is available from the CHARM (Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity) study, but an earlier study found no interaction between baseline renal function and type of HF (HFpEF vs. HFrEF) (16). In the present study, we found that in patients with clinically stable HFpEF, WRF at 8 weeks was independently associated with all cardiovascular outcomes examined and all-cause mortality. Therefore, the overall association between WRF and poor clinical outcomes in chronic HFpEF seems comparable to HFrEF and acute HF.



CENTRAL ILLUSTRATION Kaplan-Meier Curve: CV Death and HF Hospitalization Stratified According to Treatment and WRF

The Central Illustration shows the relationship between occurrence of worsening renal function (WRF), randomized treatment, and the first occurrence of cardiovascular (CV) death or heart failure (HF) hospitalization. Univariate hazard ratio (HR) versus irbesartan and no WRF, HR: 1.14 (95% confidence interval [CI]: 1.00 to 1.31), p = 0.057 for placebo and no WRF; HR: 1.46 (95% CI: 0.97 to 2.20), p = 0.073 for placebo and WRF; and HR: 1.97 (95% CI: 1.51 to 2.58), p < 0.001 for irbesartan and WRF, respectively.

TABLE 3 Multivariable Analysis: WRF and Cardiovascular Death and HF Hospitalizations

	Overall		Placebo		Irbesartan		p Value
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	Interaction*
≥0.3 mg/dl and ≥25% increase in creatinine	1.43 (1.10–1.85)	0.008	1.09 (0.66–1.79)	0.73	1.66 (1.21–2.28)	0.002	0.13
≥0.3 mg/dl increase in creatinine	1.41 (1.09–1.83)	0.009	1.19 (0.74–1.90)	0.48	1.57 (1.14–2.15)	0.005	0.26
≥20% decrease in eGFR	1.35 (1.08–1.69)	0.009	1.37 (0.95–1.99)	0.089	1.36 (1.01–1.82)	0.041	0.94

*Interaction between WRF and treatment on outcome. WRF defined at 8 weeks.
Abbreviations as in Tables 1 and 2.

RAAS INHIBITION, WRF, AND OUTCOME. It has long been known that initiation of a RAAS inhibitor may lead to an increase in SCr (and a decrease in eGFR), which is usually small (17). This is thought to occur because RAAS activation in HF leads to glomerular efferent arteriolar vasoconstriction that preserves GFR in the face of a fall in glomerular perfusion pressure. RAAS blockers can reduce glomerular perfusion pressure (by reducing systemic arterial and afferent arteriolar pressure while simultaneously preventing compensatory efferent arteriolar constriction). However, in the long run, angiotensin-converting enzyme inhibitor and angiotensin receptor blocker treatment seems to preserve or, in certain populations, attenuate decreases in eGFR, suggesting that any initial decline in GFR may not be clinically relevant (18–20). It could even be argued that the initial decrease in eGFR with RAAS inhibition serves as a marker of RAAS activation intensity and, therefore, potentially is a more favorable response to therapy. These hypotheses have been tested in retrospective analyses of multiple HFrEF/left ventricular dysfunction trials. In the SAVE (Survival and Ventricular Enlargement) trial, patients developing WRF with captopril treatment experienced a better outcome than patients developing WRF with placebo (and even better than in patients receiving placebo not developing WRF) (11). In an analysis of the 2 SOLVD (Studies of Left Ventricular Dysfunction) trials, Testani et al. (5) found that only WRF occurring with placebo was associated with mortality, whereas patients developing WRF while taking enalapril had the best outcome. Similar data exist for angiotensin receptor blockers and MRAs (6–8).

In the context of these previous studies, our findings in patients with HFpEF show some remarkable similarities and differences. First, depending on the definition used, WRF occurred in 6.0% to 14.4% of patients allocated to the irbesartan group, consistent with previous studies in HFrEF in which the incidence was approximately 6% to 10% after starting an angiotensin-converting enzyme inhibitor or

TABLE 4 WRF and Primary and Secondary Outcomes

	CV Death/HF Hospitalization			All-Cause Death			HF Hospitalization		
	Events (n/N)	HR (95% CI)	p Value	Events (n/N)	HR (95% CI)	p Value	Events (n/N)	HR (95% CI)	p Value
Univariate									
WRF*	85/229	1.75 (1.41–2.17)	<0.001	72/229	1.63 (1.28–2.08)	<0.001	60/229	1.85 (1.41–2.41)	<0.001
Irbesartan	61/153	1.97 (1.50–2.58)	<0.001	53/153	1.94 (1.45–2.59)	<0.001	42/153	2.10 (1.51–2.91)	<0.001
Placebo	24/76	1.27 (0.85–1.93)	0.25	19/76	1.18 (0.74–1.87)	0.49	18/76	1.53 (0.95–2.46)	0.082
p value interaction			0.084			0.073			0.28
Multivariate									
WRF*	85/229	1.43 (1.10–1.85)	0.008	72/229	1.41 (1.05–1.88)	0.020	60/229	1.49 (1.08–2.05)	0.002
Irbesartan	61/153	1.66 (1.21–2.28)	0.002	53/153	1.72 (1.22–2.43)	0.002	42/153	1.61 (1.08–2.38)	0.018
Placebo	24/76	1.09 (0.66–1.79)	0.73	19/76	0.99 (0.57–1.71)	0.97	18/76	1.30 (0.73–2.30)	0.37
p value interaction			0.13			0.078			0.52
Interaction									
Irbesartan and no WRF*	378/1659	Ref.		320/1659	Ref.		240/1659	Ref.	
Irbesartan and WRF*	61/153	1.68 (1.23–2.31)	0.001	53/153	1.74 (1.23–2.45)	0.002	42/153	1.63 (1.10–2.41)	0.014
Placebo and no WRF*	432/1707	1.15 (0.97–1.36)	0.15	352/1707	1.19 (0.98–1.44)	0.073	273/1707	1.10 (0.89–1.35)	0.40
Placebo and WRF*	24/76	1.23 (0.75–2.02)	0.41	19/76	1.16 (0.67–2.00)	0.60	18/76	1.43 (0.81–2.52)	0.22

*WRF is defined as ≥0.3 mg/dl and ≥25% increase in creatinine.
CV = cardiovascular; other abbreviations as in Tables 1 and 2.

angiotensin receptor blocker (and somewhat higher, at around 15%, with an MRA) (5–8). Second, initiation of a RAAS inhibitor results in an immediate but limited fall in eGFR, although thereafter eGFR falls gradually over time, at a similar rate to that in the placebo group. We also found that across the whole I-PRESERVE population, WRF was associated with poor outcome, as alluded to earlier.

However, WRF occurring after initiation of irbesartan treatment in patients with HFpEF was associated with considerably higher event rates, independent of other risk factors (a relationship not apparent in the placebo group). This finding directly contrasts with the findings from SOLVD and Val-HeFT (Valsartan Heart Failure Trial) in patients with HFrEF (5,8,21), although it is unclear why this discrepancy exists. There are some obvious differences between the trials: irbesartan did not improve outcome in I-PRESERVE, whereas both enalapril and valsartan did in SOLVD and Val-HeFT, respectively. Theoretically, the findings with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in HFrEF could represent the summed result of a negative effect of WRF outweighed by other positive effects of RAAS inhibition, resulting in a net positive effect on outcome. Because irbesartan did not improve any clinical outcome in I-PRESERVE, perhaps the negative effect of WRF was not counterbalanced sufficiently by the potentially positive effects of angiotensin receptor blocker treatment. Indeed, even patients who did not develop WRF in I-PRESERVE demonstrated no suggestion of improved outcome. It could also be that the WRF observed after RAAS blockade in patients with HFpEF reflects a different and more harmful process than WRF in HFrEF.

We found that blood pressure reduction with irbesartan was more pronounced in the WRF group and even greater compared with the blood pressure reduction in patients taking placebo who developed WRF. This finding suggests a possible reason for WRF occurrence with irbesartan but not necessarily the reason for the poor outcome. In addition, we observed significant associations between changes in MAP and eGFR, as well as a significant interaction among irbesartan, changes in MAP, and changes in eGFR. This contrasts with findings from the literature on RAAS inhibitors in patients without HF, in which greater blood pressure reductions were associated with a lower incidence of renal endpoints (20). Finally, NT-proBNP levels were higher in patients experiencing WRF in the irbesartan group. This finding could represent more pronounced venous congestion and increased renal venous pressure and, together with a decrease in MAP, could have reduced renal perfusion pressure substantially, with subsequent reduction in eGFR and increase in salt and water retention leading to poor clinical outcome (22). Future investigation of the epidemiology, pathophysiology, and treatment of HFpEF should take renal function into account.

STUDY LIMITATIONS. As a retrospective analysis of a clinical trial, observations from this study may not apply to the general HFpEF population. More importantly, I-PRESERVE demonstrated no overall effect of irbesartan treatment on outcome, and therefore analyses of subsets of patients should be regarded as hypothesis generating. For reasons unknown, repeat SCr values were not available for all patients, potentially resulting in bias, although this was the case in only a small proportion of patients. We should also consider the possibility that the observed associations are in fact chance findings given that the number of events in this HFpEF patient population was limited.

CONCLUSIONS

The incidence of WRF after initiation of an angiotensin receptor blocker in HFpEF was similar to that observed previously in HFrEF but, in contrast to patients with HFrEF, it was associated with poorer clinical outcomes.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with heart failure and reduced left ventricular ejection fraction, treatment with inhibitors of the renin-angiotensin-aldosterone system may cause worsening of renal function despite systemic hemodynamic improvement.

TRANSLATIONAL OUTLOOK: The mechanisms responsible for deterioration of renal function in some patients with heart failure and preserved ejection fraction during treatment with renin-angiotensin-aldosterone system inhibitors, and the associated worsening of prognosis that parallels the decline in renal function, require further investigation.

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KEY WORDS angiotensin receptor blocker, HFpEF, prognosis, worsening renal function

APPENDIX For supplemental tables, please see the online version of this article.