

## Proteinuria, Chronic Kidney Disease, and the Effect of an Angiotensin Receptor Blocker in Addition to an Angiotensin-Converting Enzyme Inhibitor in Patients With Moderate to Severe Heart Failure

Inder S. Anand, MD, DPhil (Oxon); Kalkidan Bishu, MD; Thomas S. Rector, PhD; Areef Ishani, MD; Michael A. Kuskowski, PhD; Jay N. Cohn, MD

**Background**—Chronic kidney disease (CKD) is an established risk factor for poor outcomes in heart failure (HF). Whether proteinuria provides additional prognostic information is not known. Renin-angiotensin blockade medications improve outcomes in HF but are underutilized in HF patients with renal dysfunction because of safety concerns and a lack of evidence of their effectiveness.

**Methods and Results**—In the Valsartan in Heart Failure Trial (Val-HeFT), 5010 patients with class II, III, or IV heart failure were randomly assigned to receive valsartan or placebo. The 2 primary outcomes were death and first morbid event, defined as death, sudden death with resuscitation, hospitalization for HF, or administration of intravenous inotropic or vasodilator drugs for 4 hours or more without hospitalization. The study cohort was divided into subgroups according to the presence of CKD (estimated glomerular filtration rate  $<60 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ ) and proteinuria (positive dipstick). Multivariable Cox proportional hazards regression models were used to examine the relationships between study outcomes and proteinuria, including its interaction with CKD. The interaction between valsartan and CKD was also tested. The effect of valsartan on estimated glomerular filtration rate was estimated by generalized linear models, including tests of interactions between treatment and CKD. At baseline, CKD was found in 58% and dipstick-positive proteinuria in 8% of patients. Dipstick-positive proteinuria was independently associated with mortality (hazard ratio [HR] 1.28, 95% confidence interval [CI] 1.01 to 1.62,  $P=0.05$ ) and first morbid event (HR 1.28, 95% CI 1.06 to 1.55,  $P=0.01$ ). The increased risk of death associated with dipstick-positive proteinuria was similar for those with and without CKD (HR 1.26, 95% CI 0.96 to 1.66 versus HR 1.37, 95% CI 0.83 to 2.26;  $P=0.94$ ), as was the hazard for first morbid event (HR 1.26, 95% CI 1.01 to 1.57 versus HR 1.42, 95% CI 0.98 to 2.07;  $P=0.71$ ). Valsartan reduced estimated glomerular filtration rate compared with placebo to a similar extent ( $P=0.52$ ) in the subgroups with CKD (mean reduction  $-3.6 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ ) and without CKD (mean reduction  $-4.0 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ ) and by  $-3.8 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$  in both groups combined. The beneficial effect of valsartan on first morbid events was similar in those with and without CKD (HR 0.86, 95% CI 0.74 to 0.99 versus HR 0.91, 95% CI 0.73 to 1.12;  $P=0.23$ ) and was significant in the subgroup with CKD. The effect of valsartan on mortality did not differ in patients with and without CKD (HR 1.01, 95% CI 0.85 to 1.20 versus HR 0.91, 95% CI 0.69 to 1.25;  $P=0.08$ ).

**Conclusions**—CKD was common and dipstick-positive proteinuria was infrequent in this sample of patients with HF. After controlling for other risk factors, including CKD, the relatively small subgroup with dipstick-positive proteinuria did have worse outcomes. Valsartan reduced the estimated glomerular filtration rate by the same amount in patients with and without CKD and reduced the risk of the first morbid event in patients with CKD, which suggests its beneficial effects in patients with HF and CKD. (*Circulation*. 2009;120:1577-1584.)

**Key Words:** heart failure ■ kidney diseases ■ proteinuria ■ clinical trial ■ angiotensin II type 1 receptor blockers ■ valsartan

Approximately 5 million Americans over the age of 20 years have heart failure (HF).<sup>1</sup> A significant proportion of these patients have concomitant chronic kidney disease (CKD), defined as an estimated glomerular filtration rate (eGFR)  $<60 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ . The prevalence of CKD has been reported to be in the range of 32% to 50% in the major chronic

HF trials.<sup>2-8</sup> Population-based surveys in North America have found a similar prevalence of 38% to 56%.<sup>9-11</sup> The presence of CKD is a significant independent risk factor for poor outcomes in patients with HF.<sup>2-11</sup> Despite the increased risk, patients with concomitant CKD are less likely to be prescribed proven HF medications such as angiotensin-converting enzyme inhibitors

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Received January 26, 2009; accepted July 15, 2009.

From the VA Medical Center (I.S.A., K.B., T.S.R., A.I.), Minneapolis, Minn; Geriatric Research, Education & Clinical Center (M.A.K.), VA Medical Center, Minneapolis, Minn; and University of Minnesota (I.S.A., K.B., T.S.R., A.I., M.A.K., J.N.C.), Minneapolis, Minn.

Correspondence to Inder S. Anand, MD, FRCPC, DPhil (Oxon), VA Medical Center, Cardiology 111-C, One Veterans Dr, Minneapolis, MN 55417. E-mail [anand001@umn.edu](mailto:anand001@umn.edu)

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*Circulation* is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIRCULATIONAHA.109.853648

(ACEIs) and angiotensin receptor blockers (ARBs).<sup>10,12</sup> Reasons for the underutilization of renin-aldosterone-angiotensin system blockade in HF patients with CKD include the lack of evidence of benefit in this population and the perception that these agents may further worsen renal function. A recent meta-analysis found that the combined use of ACEIs and ARBs was associated with an increased risk of worsening renal function, hyperkalemia, and hypotension; however, the effects on cardiovascular outcomes were not reported.<sup>13</sup> Some studies have suggested that the beneficial effect of ACEIs on cardiovascular end points in HF patients with CKD is equal to or even greater than in those without CKD.<sup>9,10,14</sup>

### Clinical Perspective on p 1584

Although much is known about CKD and HF, the role of proteinuria in HF patients has not been investigated as extensively.<sup>15–17</sup> Whereas proteinuria, a surrogate of structural kidney and vascular disease, is a marker for poor outcomes in diabetes mellitus, coronary artery disease, and hypertension,<sup>18–26</sup> the prognostic significance of proteinuria in HF has not been reported. Because there may be unique differences in the mechanisms of CKD and proteinuria in patients with HF, these variables could have independent prognostic significance. In patients with hypertension, CKD, or diabetes mellitus, the addition of an ARB in patients receiving ACEIs has been reported to reduce proteinuria.<sup>27</sup> The ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Investigators, on the other hand, recently reported that in people at high risk for vascular events, the composite of dialysis and doubling of serum creatinine was more frequent with combination therapy of the ARB telmisartan and ACEIs, despite a reduction of proteinuria.<sup>28</sup> Similar data are not available in HF patients.

In the present study, we report a secondary analysis of the Valsartan in HF Trial (Val-HeFT) database that examined the relationship between proteinuria and study end points controlling for other risk factors, including CKD. The effects of valsartan on longitudinal changes in eGFR and study end points are compared in patients who did or did not have CKD at baseline.

## Methods

### Data Source

Val-HeFT was a randomized, placebo-controlled, double-blind, multicenter trial that enrolled 5010 patients with symptomatic HF to evaluate the efficacy of the ARB valsartan. Details of the study design and results have been presented previously.<sup>29</sup> Briefly, patients were enrolled in the study who had stable, symptomatic HF, were receiving recommended HF therapy, and had a left ventricular ejection fraction <40% and a left ventricular internal diameter in diastole adjusted for body surface area  $\geq 2.9$  cm/m<sup>2</sup>. Exclusion criteria included persistent mean standing systolic blood pressure <90 mm Hg or serum creatinine >2.5 mg/dL. Eligible patients were stratified according to baseline use of a  $\beta$ -blocker and were randomly allocated to receive oral valsartan or placebo in addition to ACEIs in most cases (93%). Treatment with valsartan was initiated at 40 mg BID, and the dose was doubled every 2 weeks to reach the target dose of 160 mg BID, provided systolic blood pressure was  $\geq 90$  mm Hg, there were no signs or symptoms of hypotension, and serum creatinine levels did not exceed 150% of the baseline value.

The study had 2 primary end points: Mortality and the first morbid event, which was defined as death, sudden death with resuscitation, hospitalization for HF, or administration of intravenous inotropic or

vasodilator drugs for 4 hours or more without hospitalization. Routine laboratory tests for hematology, blood chemistries, urinalysis, and assessment of plasma norepinephrine, brain natriuretic peptide, renin activity, and aldosterone values were performed at baseline and at 4-, 12-, and 18-month follow-up visits, as well as at the end of the study. Proteinuria was measured via dipstick urinalysis in a central laboratory, and results were categorized as being positive (1+ or more) or negative for proteinuria. Any reference to proteinuria in the present report, unless otherwise specified, indicates dipstick-positive proteinuria. eGFR was calculated with the Modification of Diet in Renal Disease 6-component equation incorporating age, race, gender, and levels of serum creatinine, blood urea nitrogen, and serum albumin.<sup>30</sup>

### Data Analysis

Data are presented as mean values and SDs for continuous variables. Continuous variables with a skewed distribution are reported as median and interquartile ranges and were analyzed using the natural logarithm transformation. Categorical variables are reported as absolute numbers and percentages. ANOVA, with CKD and proteinuria as factors, including a test for interaction, was used to compare demographic and clinical characteristics of groups defined by baseline values and to identify variables that were associated with CKD or proteinuria.

Cox proportional hazards regression models were used to assess the association between the presence of CKD, proteinuria, and several other baseline variables with time to death or first morbid event. The following baseline variables were included in the Cox multivariable models in addition to proteinuria and CKD: Male gender, age  $\geq 65$  years, race, ischemic heart disease, hemoglobin, atrial fibrillation, diabetes mellitus, systolic blood pressure, pulse rate, peripheral edema, New York Heart Association functional class, left ventricular ejection fraction, plasma sodium, plasma potassium, plasma albumin, brain natriuretic peptide, neutrophil count, lymphocyte count, norepinephrine, aldosterone, plasma renin activity; use of digoxin, an ACEI, a  $\beta$ -blocker, aspirin, spironolactone, or a diuretic; and randomly assigned treatment (valsartan or placebo). The interactions between proteinuria and CKD and between valsartan and CKD were of particular interest. The numbers needed to treat were calculated in those with and without CKD for first morbid event by the method of Altman and Andersen.<sup>31</sup>

Calculated changes in eGFR within each treatment group (valsartan, placebo) were compared with generalized linear models with a normal probability distribution, identity link function, and unstructured correlation matrix for repeated assessments of eGFR. Various models included treatment (valsartan, placebo), presence of CKD at baseline, and time (with dummy variables used to represent data collected at 4, 12, and 24 months) and their interactions. Changes in hemoglobin at 4 months within each treatment group (valsartan, placebo) were compared with ANOVA for repeated measures with an interaction between treatment and baseline CKD.

All analyses were performed with SPSS 15 (SPSS Inc, Chicago, Ill). All tests are presented with 2-sided *P* values, and values <0.05 were considered significant.

## Results

### Baseline Characteristics

A total of 5010 patients were randomized in Val-HeFT, with 2511 assigned to valsartan and 2499 to placebo. The overall mean duration of follow-up was 23 months (range 0 to 38 months). There were 5002 patients who had baseline eGFR values, and 4958 patients had urinalysis at baseline. CKD, defined as eGFR <60 mL · min<sup>-1</sup> · 1.73 m<sup>-2</sup>, was found in 2916 patients (58%) at baseline. Dipstick proteinuria was positive in 405 patients (8.2%). There were 116 patients (2.3%) with proteinuria and no CKD, 2601 (52%) with CKD and no proteinuria, and 289 (5.8%) with combined proteinuria

**Table 1. Baseline Characteristics According to Presence or Absence of Proteinuria and CKD**

	No CKD, No Pr	CKD, No Pr	Pr, No CKD	CKD and Pr	ANOVA		
					CKD	Pr	Interaction
No. of patients	1951	2601	116	289			
Mean age, y, mean (SD)	58 (11)	66 (9)	59 (12)	65 (10)	<0.001	0.06	0.76
Men, n (%)	1345 (69)	2303 (89)	76 (66)	240 (83)	<0.001	0.04	0.64
White, n (%)	1761 (90)	2381 (92)	81 (94)	240 (83)	0.33	<0.001	0.83
Physical examination							
Mean BMI, kg/m <sup>2</sup> (SD)	27 (4.9)	27 (4.1)	27 (5.3)	27 (4.2)	0.28	0.67	0.48
Mean SBP, mm Hg (SD)	124 (18)	123 (18)	129 (19)	131 (19)	0.63	<0.001	0.12
Mean DBP, mm Hg (SD)	77 (10)	74 (10)	80 (11)	79 (11)	0.001	<0.001	0.29
Mean HR, bpm (SD)	74 (12)	72 (12)	81 (14)	76 (14)	<0.001	<0.001	0.04
NYHA class 3 and 4, n (%)	622 (32)	1060 (41)	59 (51)	147 (51)	0.11	<0.001	0.11
PND, n (%)	150 (8)	232 (9)	17 (15)	41 (14)	0.82	<0.001	0.6
Elevated JVP, n (%)	219 (11)	346 (13)	26 (22)	75 (26)	0.14	<0.001	0.69
Peripheral edema, n (%)	299 (15)	449 (17)	31 (27)	84 (29)	0.32	<0.001	0.93
S3, n (%)	508 (26)	636 (25)	48 (41)	92 (32)	0.03	<0.001	0.11
Orthopnea, n (%)	225 (12)	369 (14)	22 (19)	61 (21)	0.09	<0.001	0.9
Comorbidities, n (%)							
Ischemic cause of HF	1025 (53)	920 (35)	60 (52)	117 (41)	<0.001	0.44	0.29
Diabetes mellitus	381 (20)	685 (26)	40 (35)	156 (54)	<0.001	<0.001	0.009
Atrial fibrillation	164 (8)	367 (14)	16 (14)	49 (17)	0.02	0.03	0.49
Hypertension	124 (6)	170 (7)	8 (7)	28 (10)	0.3	0.19	0.36
Laboratory values							
Mean eGFR, mL · min <sup>-1</sup> · 1.73 m <sup>-2</sup> (SD)	72.3 (11)	48 (9)	73 (12)	46 (10)	<0.001	0.33	0.005
Mean hemoglobin, g/dL (SD)	13.8 (1.3)	13.6 (1.5)	13.8 (1.7)	13.5 (1.8)	0.003	0.1	0.61
Mean serum albumin, g/dL (SD)	4.2 (0.3)	4.2 (0.3)	4 (0.4)	3.9 (0.4)	<0.001	<0.001	0.02
Median CRP, mg/L (IQR)	2.8 (1.1–7.1)	3.3 (1.6–7.6)	4.3 (1.9–7.9)	5.8 (2.8–10.3)	0.001	<0.001	0.19
Median norepinephrine, pg/mL (IQR)	342 (240–501)	430 (301–611)	400 (254–585)	432 (301–665)	<0.001	0.04	0.33
Median aldosterone, pg/mL (IQR)	92 (59–152)	116 (68–198)	101 (57–169)	121 (73–207)	<0.001	0.71	0.43
Median BNP, pg/mL (IQR)	65 (28–147)	122 (52–273)	150 (44–398)	253 (107–467)	<0.001	<0.001	0.84
Median PRA, ng · mL <sup>-1</sup> · h <sup>-1</sup> (IQR)	4.2 (1.4–13.0)	6.9 (2.1–20.7)	2.0 (0.9–8.8)	2.65 (1.1–10.1)	0.006	<0.001	0.17
Mean uric acid, mg/dL (SD)	6.6 (1.7)	8.1 (2.2)	6.9 (1.9)	8.2 (2.1)	<0.001	0.04	0.5
Mean serum sodium, mEq/L (SD)	139.4 (2.7)	139.4 (3.1)	139.6 (3.7)	139.5 (3.5)	0.66	0.37	0.95
Mean serum potassium, mEq/L (SD)	4.3 (0.6)	4.5 (0.6)	4.3 (0.6)	4.5 (0.7)	<0.001	0.26	0.69
Mean LVEF, % (SD)	27 (7)	27 (7)	26 (7)	26 (7)	0.61	0.03	0.18
Medications, n (%)							
ACEI	1821 (93)	2399 (92)	112 (97)	259 (90)	0.007	0.84	0.05
β-Blocker	716 (37)	875 (34)	49 (42)	92 (32)	0.01	0.49	0.18
Diuretic	1532 (79)	2336 (90)	101 (87)	268 (93)	<0.001	0.004	0.16
Digoxin	1328 (68)	1693 (65)	95 (82)	221 (77)	0.12	<0.001	0.65
Spironolactone	54 (3)	168 (7)	8 (7)	14 (5)	0.51	0.31	0.02

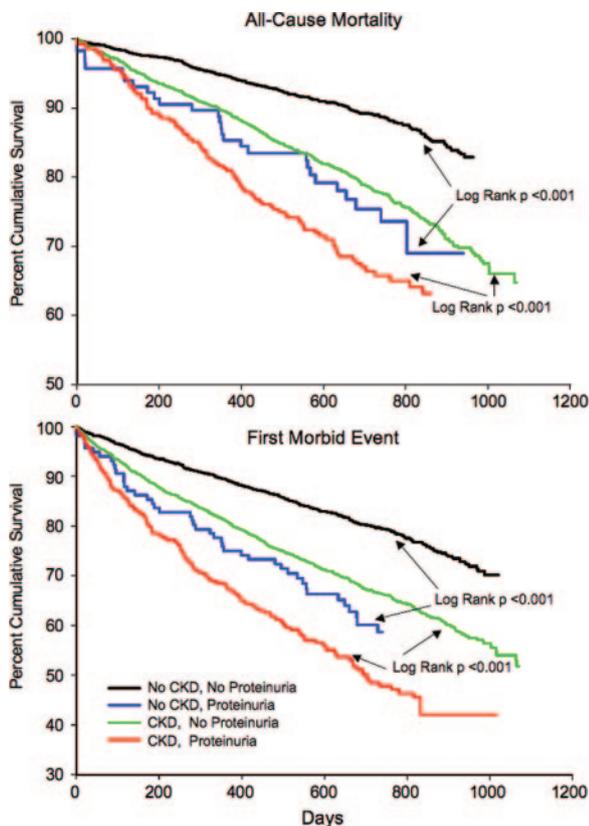
Pr indicates proteinuria; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; NYHA, New York Heart Association; PND, paroxysmal nocturnal dyspnea; JVP, jugular venous pressure; CRP, C-reactive protein; IQR, interquartile range; BNP, brain natriuretic peptide; PRA, plasma renin activity; and LVEF, LV ejection fraction.

There were 8 patients with missing baseline eGFR. ANOVA with CKD and proteinuria as factors, including a test for interaction, was used to compare the demographic and clinical characteristics and identify variables that were associated with CKD and/or proteinuria.

and CKD. CKD was more prevalent in those with proteinuria (289/405 [72%] versus 2601/4552 [48%], *P*<0.001).

As summarized in Table 1, patients with CKD at baseline were more likely to be older males with atrial fibrillation. Their diastolic but not their systolic blood pressures were

lower on average. They also had worse neurohormonal and proinflammatory profiles, lower hemoglobin, and higher potassium. Those with CKD were more likely to be taking diuretics and only slightly less likely to be receiving ACEIs, probably because most patients were taking ACEIs as re-



**Figure 1.** Kaplan–Meier curves for time to death and first morbid event according to presence or absence of proteinuria and CKD. Proteinuria was associated with worse outcomes regardless of CKD. Log-rank tests  $P < 0.001$ .

quired by the protocol as a standard of care. Some of the baseline characteristics of patients with proteinuria were different from those with CKD. Patients with proteinuria were associated with higher systolic and diastolic blood pressures, whereas patients with CKD were associated with lower diastolic pressures. Proteinuria was associated with physical examination and clinical indicators of volume overload, including paroxysmal nocturnal dyspnea, elevated jugular venous pressure, peripheral edema, third heart sound, orthopnea, and higher New York Heart Association class, whereas no such relationships were observed with CKD. Proteinuria was associated with lower plasma renin activity, whereas CKD was associated with higher levels of plasma renin activity. Mean uric acid was slightly greater in the presence of proteinuria but much more elevated in the presence of CKD.

### Association of Baseline Proteinuria With Clinical Outcomes

Proteinuria was associated with an increased risk of mortality (unadjusted hazard ratio [HR] 1.76, 95% CI 1.46 to 2.13) and first morbid event (unadjusted HR 1.86, 95% CI 1.60 to 2.17). Figure 1 shows the unadjusted relationship between proteinuria and all-cause mortality and first morbid event in the subgroups with and without CKD. Patients with proteinuria had worse prognosis than those without proteinuria in both subgroups. Proteinuria was independently associated with mortality (HR 1.28, 95% CI 1.01 to 1.62,  $P = 0.05$ ) and the first morbid event (HR 1.28, 95% CI 1.06 to 1.55,  $P = 0.01$ ) after adjustment for other prognostic variables, including CKD. The mortality hazard ratio for dipstick-positive proteinuria was similar for those with and without CKD (HR 1.26, 95% CI 0.96 to 1.66 versus HR 1.37, 95% CI 0.83 to 2.26;  $P$  for interaction = 0.94), as was the hazard for first morbid event (HR 1.26, 95% CI 1.01 to 1.57 versus HR 1.42, 95% CI 0.98 to 2.07;  $P$  for interaction = 0.71), which indicates that the effect of proteinuria was similar in those with or without CKD when adjustments were made for other prognostic variables (Table 2).

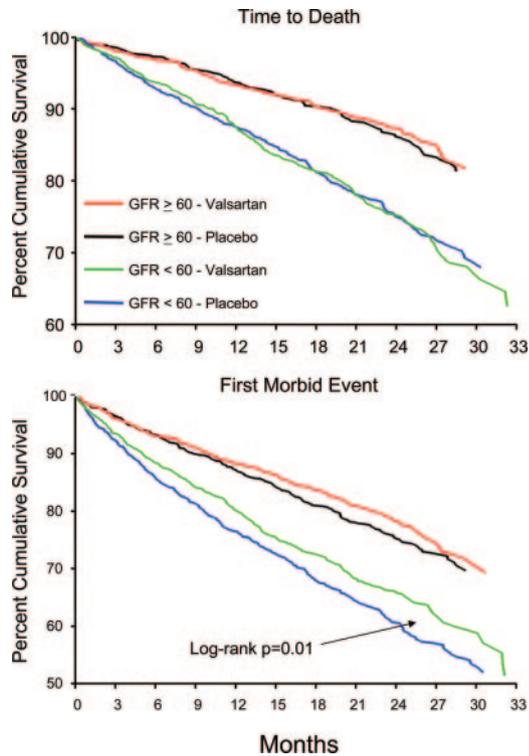
### Effect of Valsartan on Outcomes

Figure 2 shows the Kaplan–Meier curves for time to death and first morbid event according to treatment and CKD. Valsartan had no effect on mortality in either subgroup defined by CKD but did appear to reduce first morbid events when CKD was present. With adjustment for any differences in other risk factors in a Cox hazards model, valsartan therapy was associated with a reduction in the first morbid event (HR 0.86, 95% CI 0.74 to 0.99) in the subgroup of patients with baseline CKD. In patients without CKD, the reduction in first morbid event seen with valsartan was similar but not significant (HR 0.91, 95% CI 0.73 to 1.12; Table 3). The probability value for interaction between valsartan treatment and presence or absence of CKD was not significant, which suggests that the effect of valsartan did not clearly differ in patients with or without CKD. However, the estimated numbers of patients needed to treat for 1 year to prevent 1 first morbid event were 35 for patients with underlying CKD versus 100 for those with no CKD. As in the overall trial, valsartan did not significantly affect mortality in the smaller subgroups with and without CKD (HR 1.01, 95% CI 0.85 to 1.20 versus HR 0.91, 95% CI 0.69 to 1.25;  $P$  for interaction = 0.08).

**Table 2. Adjusted HRs\* (95% CIs) for Mortality and First Morbid Event Grouped by Presence of Proteinuria and CKD at Baseline**

	Death			First Morbid Event		
	HR	95% CI	<i>P</i>	HR	95% CI	<i>P</i>
Proteinuria with CKD in model	1.28	1.01–1.62	0.05	1.28	1.06–1.55	0.01
Proteinuria in subgroup without CKD	1.37	0.83–2.26		1.42	0.98–2.07	
Proteinuria in subgroup with CKD	1.26	0.96–1.66		1.26	1.01–1.57	
Interaction between proteinuria and CKD	...	...	0.94	...	...	0.71

\*Cox proportional hazards regression models were used to assess the association between the presence of CKD and proteinuria with time to death or first morbid event. Baseline variables were included as covariates. The interaction  $P$  value compares the HR in the 2 subgroups. See Methods for a complete list of covariates.



**Figure 2.** Kaplan–Meier curves for time to death or first morbid event according to treatment group and baseline CKD. Valsartan had a significant effect on time to first morbid event in the presence of CKD. Log-rank test  $P=0.01$ . GFR indicates glomerular filtration rate.

**Effect of Valsartan on eGFR**

The effect of valsartan on eGFR by baseline renal function in patients with an eGFR available at various time points is summarized in Table 4. Differences in the valsartan effect in those with and without CKD at baseline did not vary significantly with time. After pooling over all time points, valsartan was associated with a placebo-adjusted reduction in eGFR in both those who did ( $-3.6 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ ) and did not ( $-4.0 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ ) have CKD at baseline, and the difference in valsartan effects was not significant between the 2 groups ( $P=0.52$ ). The estimated mean  $\pm$  SE decrease in eGFR in the valsartan group was  $-6.7 \pm 0.2$  versus  $-2.9 \pm 0.2 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$  in the placebo group ( $P<0.001$ ). The estimated mean valsartan effect of eGFR was  $-3.8 \pm 0.2 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$  when the groups with and without CKD at baseline were combined.

Interestingly, although the present data on subjects with proteinuria were much more limited than for those with CKD, in a similar analysis, the effect of valsartan on eGFR was significantly different in patients who did or did not have proteinuria at baseline. The decrease in eGFR in the group without proteinuria was  $-2.6 \pm 0.2 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$  in the placebo group versus  $-6.5 \pm 0.2 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$  in the valsartan group, with a mean difference of  $-3.9 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ . The decrease in eGFR in the group with proteinuria was  $-5.3 \pm 0.6 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$  in the placebo group versus  $-6.6 \pm 0.6 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$  in the valsartan group, with a mean difference of  $-1.3 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ , which was a significantly smaller decrease than in the group without proteinuria ( $-1.3$  versus  $-3.9 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ ,  $P=0.004$ ). These data also suggest that valsartan did not attenuate the decrease in eGFR over time in patients with proteinuria (placebo  $-5.3 \pm 0.6 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$  versus valsartan  $-6.6 \pm 0.6 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ ).

**Treatment Discontinuation and Safety**

Overall permanent discontinuation of the assigned treatment was seen more often in the valsartan group ( $n=247$ , 9.8%) than in the placebo group ( $n=180$ , 7.2%; difference 2.6%,  $P<0.001$ ). In patients with CKD at baseline, the permanent discontinuation rate was higher in the valsartan group ( $n=186$ , 12.6%) than in the placebo group ( $n=132$ , 9.2%; difference 3.4%;  $P=0.002$ ). The discontinuation rate was lower and not significantly different between treatment groups among patients without CKD at baseline (valsartan 5.9% versus placebo 4.5%; difference=1.4%,  $P=0.17$ ). The incidence of hyperkalemia with treatment with valsartan was higher in the group of patients with CKD at baseline (valsartan 8.5% versus placebo 4.5%; difference=4%,  $P<0.001$ ).

Valsartan reduced hemoglobin independent of CKD. The mean placebo-adjusted effect of valsartan after 4 months was  $-0.37 \text{ g/dL}$  in the group without CKD versus  $-0.36 \text{ g/dL}$  in the group with CKD ( $P$  for interaction=0.45). Overall, the mean decrease in hemoglobin in the valsartan group after 4 months was  $-0.4 \pm 0.02 \text{ g/dL}$  versus  $-0.03 \pm 0.02 \text{ g/dL}$  in the placebo group ( $P<0.001$ ). Initiation of dialysis was not reported for any participant in Val-HeFT.

**Discussion**

National Kidney Foundation criteria<sup>32</sup> were used to define CKD as an eGFR  $<60 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ . By this definition, 58% of Val-HeFT patients with stable New York

**Table 3. Effect of Valsartan on Mortality and First Morbid Event by Renal Function**

End Point	Valsartan, n (%)	Placebo, n (%)	HR (95% CI)	Interaction <i>P</i>
<b>Death</b>				
Without CKD	132 (12.8)	141 (13.4)	0.91 (0.69–1.25)	0.08
With CKD	362 (24.5)	341 (23.7)	1.01 (0.85–1.20)	
<b>First morbid event</b>				
Without CKD	222 (21.6)	250 (23.7)	0.91 (0.73–1.12)	0.23
With CKD	499 (33.8)	549 (38.1)	0.86 (0.74–0.99)	

Cox proportional hazards regression models were used to assess the association between the presence of CKD and treatment group with time to death or first morbid event. Baseline variables were included as covariates. See Methods for a complete list of covariates.

**Table 4. Effect of Valsartan on eGFR by Presence or Absence of CKD at Baseline**

	No.	Placebo	Valsartan	Difference±SEM
Model 1: Discrete times				
No. after 4 mo	4469	2260	2209	
Without CKD	1922	-3.1±0.3	-6.9±0.3	-3.8±0.4
With CKD	2547	-0.2±0.2	-3.9±0.2	-3.7±0.3
No. after 12 mo	3934	2007	1927	
Without CKD	1749	-3.8±0.3	-7.9±0.4	-4.1±0.5
With CKD	2185	-1.2±0.2	-4.8±0.3	-3.6±0.3
No. after 24 mo	2040	1026	1014	
Without CKD	938	-6.4±0.5	-10.3±0.5	-4.3±0.7
With CKD	1102	-3.0±0.3	-6.2±0.3	-3.2±0.5
Model 2: All times				
No.	10 443	5293	5150	
Without CKD	4609	-4.4±0.3	-8.4±0.3	-4.0±0.4
With CKD	5834	-1.4±0.2	-5.0±0.2	-3.6±0.3
Model 3: Overall				
No.	10 443	-2.9±0.2	-6.7±0.2	-3.8±0.3

Data are summarized as the estimated mean±SEM change in eGFR in mL · min<sup>-1</sup> · 1.73 m<sup>-2</sup>. There were 4564 subjects, with 1 to 3 measurements of change in eGFR per subject.

Model 1: Generalized linear regression model of calculated changes in eGFR including treatment (placebo, valsartan), baseline CKD (present or absent), and time (dummy variables for 4 and 12 months, with 24 months as the reference group) and their 2-way and 3-way interactions. The 3-way interactions between treatment, CKD, and 2 dummy variables representing the 3 times points were not statistically significant ( $P=0.49$  and  $0.69$ ) and were dropped. Thereafter, the 2-way interactions between treatment and time points ( $P=0.45$  and  $0.37$ ) remained insignificant and were also dropped for model 2. The 2-way interaction between treatment and CKD in model 2 was not significant, which indicated that the effect of valsartan on eGFR was not statistically different ( $P=0.52$ ) between the groups with or without CKD at baseline. All nonsignificant interactions between treatment and other factors were omitted from model 3 to estimate the overall effect of valsartan on eGFR that was statistically significant ( $P<0.001$ ).

Heart Association functional class II to IV HF patients had CKD, despite the exclusion of patients with serum creatinine >2.5 mg/dL from the trial. The 58% prevalence of CKD in the Val-HeFT cohort is higher than the 32% to 46% reported from the SOLVD (Studies Of Left Ventricular Dysfunction), DIG (Digitalis Investigation Group), SAVE (Survival And Ventricular Enlargement), and CHARM (Candesartan in Heart failure—Assessment of Reduction in Mortality and morbidity) trials, which used similar inclusion criteria.<sup>3–5</sup> The reasons for these differences are not known.

### Proteinuria and Heart Failure

Although proteinuria is a marker of kidney disease and an important risk factor in the general population, as well as for patients with diabetes mellitus and coronary artery disease,<sup>18,26,33–35</sup> few studies have assessed the presence of proteinuria during HF. We found that 8% of patients in Val-HeFT had dipstick proteinuria. Dipstick proteinuria is a qualitative measure of urine albumin and correlates with proteinuria  $\geq 150$  mg/24 h.<sup>36</sup> Van de Wal et al<sup>15</sup> studied 94 stable chronic HF patients (New York Heart Association class III/IV); microalbuminuria was present in 32%, and only 5% of the patients had macroalbuminuria, similar to the findings in the present study.

The present secondary analysis was not designed to determine the causes of proteinuria in patients with HF. Patients with proteinuria had higher blood pressure and significantly lower serum albumin, which suggests perhaps a structural basis for proteinuria. These patients also had evidence of

worse HF with more fluid retention. In particular, a much greater percentage had an elevated jugular venous pressure, peripheral edema, paroxysmal nocturnal dyspnea, third heart sound, and orthopnea, whereas mean plasma renin activity was much lower when proteinuria was present, which suggests a possible pathogenetic role of increased intravascular volume. Wegria et al<sup>37</sup> found that unilateral elevation of renal vein pressure by application of a clamp to the renal vein of adult mongrel dogs caused proteinuria to appear from the affected kidney in 21 of 32 dogs. Proteinuria resolved completely after release of the clamp, which suggests that elevated venous pressure may be related to the proteinuria seen in HF patients. At least 2 studies have reported development of proteinuria during acute decompensated HF that was reversible after treatment.<sup>17,38</sup> However, well-designed prospective studies are required to assess the contributions of structural kidney disease, hemodynamic factors, and neurohormonal factors to the development of proteinuria in patients with HF.

An important finding in the present study, reported for the first time to the best of our knowledge, is that a simple measure of proteinuria was associated with increased morbidity and mortality in patients with HF, independent of other prognostic factors, including CKD. We could not determine why proteinuria added independent prognostic information in patients with HF. Although CKD and proteinuria shared many similar baseline correlates, there were several differences in the direction and magnitude of the baseline characteristics. As discussed above, some variables, such as an

elevated venous pressure, may have a unique relation to proteinuria and contribute to its independent relationship to adverse outcomes. However, it is also possible that the multivariable regression analyses might not have adequately controlled for all baseline differences.

### Effect of CKD on Response to Valsartan

Another important finding of the present study is that patients with CKD obtain similar relative but greater absolute benefit in long-term outcomes than do those without CKD. The number needed to treat with valsartan to prevent 1 morbid event was substantially less for patients with underlying CKD than for those with normal underlying kidney function. Similar findings were reported for ACEIs by the SAVE investigators, who found that the number needed to treat to prevent 1 cardiovascular death, myocardial infarction, or development of HF during the duration of the trial was 9 for patients with CKD and 19 for those without CKD.<sup>14</sup> These findings highlight the clinical importance of several studies that have shown an underutilization of ACEIs and ARBs in HF patients with underlying CKD. The decline in eGFR with valsartan was similar in the groups with and without CKD. The findings of the present study further indicate that HF patients with CKD who remain symptomatic with ACEI treatment are more likely to benefit from the addition of an ARB, with a slight increase in discontinuation of therapy and hyperkalemia.

### Strengths and Limitations

There are a number of strengths to the present study. We used a large contemporary population that is well treated for HF. In addition, we were able to adjust for comorbidities, cardiac function, laboratory data, medication usage, and neurohormones. Finally, unlike previous studies, we were able to determine discontinuation rates by drug and by level of kidney function. However, there are also a number of limitations. The study, by design, excluded patients with serum creatinine >2.5 mg and thus did not include patients with more severe CKD. We used dipstick urinalysis, which is a qualitative, less accurate, and less sensitive measure of urinary albumin excretion. The fairly small number of patients with dipstick-positive proteinuria was not subdivided according to degree of proteinuria. Moreover, this was a secondary analysis of a randomized controlled trial. There may have been residual confounding by unmeasured confounders despite the multivariate analysis, as well as some spurious differences. Finally, the outcomes of the present study were seen in the setting of a rigorous randomized controlled trial. Application of our findings to clinical practice may be associated with greater adverse effects than we have estimated, because patients might not meet the same risk-selection criteria or be followed up as closely, which potentially could make the risk-benefit ratio less favorable.

### Conclusions

Moderate to severe CKD is common in moderate to severe HF. Proteinuria is less frequent but is an independent risk factor in HF patients. Proteinuria appeared to be associated with surrogate measures of volume overload. Beneficial effects of valsartan when added to background HF therapy that included ACEIs were seen in those with CKD. Given

worse outcomes in those with CKD, the absolute benefit of valsartan therapy is likely to be greater than observed in those without CKD. Valsartan appeared to be well tolerated in those with CKD when added to background HF therapy, including in most patients who already tolerated ACEI therapy. Hence, efforts should be made to encourage the use of these agents in all patients who might benefit.

### Sources of Funding

This work was supported by a grant from Novartis Pharmaceuticals AG, Basel, Switzerland.

### Disclosures

Dr Anand reports research grant support from Novartis. Dr Anand has been a speaker for Novartis. Dr Cohn reports research grant support from Novartis. Dr Rector was supported in part by VA Health and Clinical Services Research and Development Grants HFP-98-001 and 04S-CROCOE-001. The views expressed herein do not necessarily represent the Department of Veterans Affairs. The remaining authors report no conflicts.

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### CLINICAL PERSPECTIVE

Chronic kidney disease (CKD) is an established risk factor for poor outcomes in heart failure. Whether proteinuria provides additional prognostic information is not known. Renin-angiotensin blockade medications improve outcomes in heart failure but are underutilized in heart failure patients with renal dysfunction because of safety concerns and a lack of evidence of their effectiveness. In this secondary analysis of the Valsartan in Heart Failure Trial (Val-HeFT), we found that CKD (glomerular filtration rate  $<60 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ ) was common (58%) and dipstick-positive proteinuria was infrequent (8%) in this population of patients with heart failure. After controlling for other risk factors, including CKD, we found that proteinuria was an independent risk factor for adverse outcomes, and its presence increased mortality by 28%. Valsartan, when added to background therapy with angiotensin-converting enzyme inhibitors, reduced the estimated glomerular filtration rate compared with placebo to a similar extent in the subgroups with and without CKD; however, the beneficial effect of valsartan on the first morbid event tended to be greater in those with CKD than in those without CKD. The estimated numbers of patients needed to treat for 1 year to prevent 1 first morbid event were 35 for patients with underlying CKD versus 100 for those with no CKD. Valsartan appeared to be well tolerated in patients with CKD when added to background heart failure therapy, and most of these patients were already receiving an angiotensin-converting enzyme inhibitor. Given worse outcomes in those with CKD, the absolute benefit of valsartan therapy is likely to be greater than observed in those without CKD. Hence, efforts should be made to encourage the use of these agents in all patients who remain symptomatic despite treatment with angiotensin-converting enzyme inhibitors, irrespective of the presence or absence of CKD.