Circulation
Heart Failure
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

Learn and Live

Is Worsening Renal Function an Ominous Prognostic Sign in Patients With Acute Heart Failure? : The Role of Congestion and Its Interaction With Renal Function

Marco Metra, Beth Davison, Luca Bettari, Hengrui Sun, Christopher Edwards, Valentina Lazzarini, Barbara Piovanelli, Valentina Carubelli, Silvia Bugatti, Carlo Lombardi, Gad Cotter and Livio Dei Cas

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circheartfailure.ahajournals.org/content/5/1/54.full

Is Worsening Renal Function an Ominous Prognostic Sign in Patients With Acute Heart Failure?
The Role of Congestion and Its Interaction With Renal Function

Marco Metra, MD; Beth Davison, PhD; Luca Bettari, MD; Hengrui Sun, MD;
Christopher Edwards, BS; Valentina Lazzarini, MD; Barbara Piovanelli, MD; Valentina Carubelli, MD;
Silvia Bugatti, MD; Carlo Lombardi, MD; Gad Cotter, MD; Livio Dei Cas, MD

Background—Worsening renal function (WRF), traditionally defined as an increase in serum creatinine levels ≥0.3 mg/dL, is a frequent finding in patients with acute heart failure (AHF) and has been associated with poorer outcomes in some but not all studies. We hypothesized that these discrepancies may be caused by the interaction between WRF and congestion in AHF patients.

Methods and Results—We measured serum creatinine levels on a daily basis during the hospitalization and assessed the persistence of signs of congestion at discharge in 599 consecutive patients admitted at our institute for AHF. They had a postdischarge mortality and mortality or AHF readmission rates of 13% and 43%, respectively, after 1 year. Patients were subdivided into 4 groups according to the development or not of WRF and the persistence of ≥1 sign of congestion at discharge. Patients with WRF and no congestion had similar outcomes compared with those with no WRF and no congestion, whereas the risk of death or of death or AHF readmission was increased in the patients with persistent congestion alone and in those with both WRF and congestion (hazard ratio, 5.35; 95% confidence interval, 3.0–9.55 at univariable analysis; hazard ratio, 2.44; 95% confidence interval, 1.24–4.18 at multivariable analysis for mortality; hazard ratio, 2.14; 95% confidence interval, 1.39–3.3 at univariable analysis; and hazard ratio, 1.39; 95% confidence interval, 0.88–2.2 at multivariable analysis for mortality and rehospitalizations).

Conclusions—WRF alone, when detected using serial serum creatinine measurements, is not an independent determinant of outcomes in patients with AHF. It has an additive prognostic value when it occurs in patients with persistent signs of congestion. ***(Circ Heart Fail.* 2012;5:54-62.)**

Key Words: renal function ■ acute heart failure ■ creatinine ■ congestion

Acute heart failure (AHF) is the most important cause of hospitalization in the United States and Europe.[1–3] It is associated with high in-hospital and postdischarge mortality and rehospitalization rates. Persistence of signs of congestion and renal dysfunction have been consistently shown to be among the most important prognostic variables.[2,4–10] Worsening renal function (WRF), usually defined as an increase in serum creatinine levels ≥0.3 mg/dL from values at admission, has also been shown to be an independent prognostic determinant.[8,10–17] Most of these data were, however, based on retrospective analyses and they are, therefore, subject to a "detection bias." For example, sicker patients who are more congested and have a longer hospital stay tend to have more creatinine measurements done and hence have a greater likelihood of showing a creatinine increase. Second, increases in serum creatinine levels may just be caused by renal hemodynamic abnormalities and diuretic therapy.[2,4,18] In all of these cases, an increase in serum creatinine would be simply a marker of more severe HF rather than of real WRF. In accordance with this hypothesis, studies based on serial measurements of serum creatinine levels, done independently from patients' clinical conditions, have failed to show a prognostic value for the changes of this variable, different from absolute serum creatinine levels, either on admission or at discharge.[6,19–21]

Clinical Perspective on p 62

WRF, as currently defined, based on changes in serum creatinine levels, may have a different prognostic significance based on HF severity and, namely, persistence of fluid overload. We, therefore hypothesized that an interaction could be shown between changes in serum creatinine levels (ie, WRF) and signs of congestion with regards of their association with patient outcomes. With this aim, clinical signs of congestion and serum creatinine levels were serially measured, on a daily basis, in consecutive patients hospitalized for AHF.

Methods

Patients

This was a study with the aim of assessing the relationship between WRF, clinical signs, and prognosis of the patients admitted for AHF. All the patients hospitalized with a diagnosis of AHF and evaluated and treated by the authors (Drs Metra, Piovanelli, Bugatti, Lombardi, Bettari, Carubelli, and Lazzarini) between January 2005 and August 2009 at the Institute of Cardiology of the University and Civil Hospital of Brescia were included into the study. AHF was diagnosed based on the typical symptoms and signs (ie, dyspnea at rest or minimal effort with signs of pulmonary and/or peripheral congestion) with need of ≥40 mg intravenous furosemide administration. We excluded patients with symptoms and/or ECG signs suggestive of acute coronary syndrome or with arrhythmia, myocarditis, valve stenosis, cardiac tamponade, aortic dissection, sepsis, or noncardiovascular factors as the main cause of symptoms.

Each patient could only contribute once to the database, and, if multiply admitted, only the first hospitalization occurring during the period under review was considered in this analysis. Patients enrolled in randomized, multicenter, intervention trials were also excluded from the study.

The study was approved by the local ethics committee of the hospital of Brescia as an observational study. Informed consent was requested and obtained from each patient recruited before entry into the study.

Measurements

Each patient underwent a complete clinical and laboratory examination at the time of admission and during hospitalization. Namely, signs of congestion (see below) and serum creatinine levels were assessed and recorded on a daily basis from the time of admission until discharge. Glomerular filtration rate (in mL/min) was estimated daily using the simplified Modification of Diet in Renal Disease equation.[22] A Doppler echocardiogram was performed during the hospitalization to evaluate the systolic left ventricular (LV) function and the presence of a restrictive LV filling pattern.

Definitions

Congestion was defined as the persistence of 1 or more signs or symptoms of fluid overload at discharge. The following symptoms and signs were prospectively considered: third heart sound, pulmonary rales, jugular venous stasis, hepatomegaly, and peripheral edema. WRF was defined by an absolute increase in serum creatinine of ≥0.3 mg/dL from the values measured at the time of admission. Patients were subdivided in 4 groups, based on the presence or not of signs of congestion at the time of discharge and on the detection of WRF during hospitalization. The 4 groups were the following: no signs of congestion and no WRF (no congestion/no WRF), congestion and no WRF (congestion/no WRF), WRF in the absence of congestion (no congestion/WRF), and both persistence of congestion and WRF (congestion/WRF). A history of chronic kidney disease was defined based on a history of an estimated glomerular filtration rate <60 mL/min per 1.73 m².[23]

With respect of the follow-up data, hospitalization was defined as any unplanned admission to hospital which required an overnight stay. Hospitalizations were classified as caused by HF when they were caused by worsening symptoms of HF with signs of fluid overload and intravenous furosemide treatment.

Follow-Up

Patients were followed with clinical visits or telephone contacts. The frequency of follow-up visits was left at the discretion of the physicians taking care of the patients. However, follow-up information was obtained at 3-month intervals, and only 1 patient was lost to follow-up. Death and HF hospitalizations were the end points of the study. The composite of death or HF rehospitalization through 1 year was the primary end point of the study. Patients who underwent heart transplantation were censored at the time of this procedure. Urgent heart transplantation was considered as an end-point, equivalent to death caused by HF.

Statistical Analysis

Values of mean±SD are presented for continuous variables and n (%) for discrete variables unless otherwise specified. Continuous variables were shown as median and interquartile range (IQR) when they had a skewed distribution. A probability value <0.05 was considered statistically significant.

Patient characteristics were compared among groups, using 1-way ANOVA or the Kruskal-Wallis test for continuous variables and the Cochran-Mantel-Haenszel χ^2 for discrete variables.

Two end points were considered to assess the outcome: all-cause mortality through 1 year (365 days) from discharge and the combined end point of all-cause mortality or hospitalization for HF through 1 year from discharge. Urgent heart transplant was considered equivalent to death for these models. Variables related to outcome at univariable analysis were entered into a multivariable Cox regression model. Variables that were collinear with another variable or that had a 10% or more missing values were excluded from consideration; the presence of an implantable cardioverter-defibrillator or CRT and the use of medications were also excluded from consideration in the models because they may be influenced by the other variables. Indicators for the 4 WRF/congestion groups were forced into the models. Multivariable models were constructed from variables having significant associations, with the outcome with $P \leq 0.05$ using backward selection with a 0.05 significance level for keeping. Linearity of the association of each predictor and the log hazard of the outcome was checked by significance of nonlinear terms for a restricted cubic spline transformation. Variables with a significantly nonlinear association were modeled with the use of a restricted cubic spline transformation. The association of each variable with the outcome is expressed as hazard ratio (HR) and 95% confidence interval (CI). For continuous variables, the HR is presented for the 75th versus the 25th percentile of the variable's overall distribution. Cumulative survival estimates were calculated using the Kaplan-Meier method. All the analyses were performed using SAS release 9.2 (SAS Institute, Inc, Cary, NC).

Results

Patient Characteristics

Five hundred ninety-nine consecutive patients admitted for AHF were included in this study. Five patients who died on or before discharge from the initial hospitalization and 1 patient lost to follow-up were excluded from the analyses. The characteristics of the remaining patients who were followed up for postdischarge events are shown in Table 1.

Compared with the others, patients with no WRF/no congestion were younger, less likely to be male, to have coronary artery disease, chronic obstructive pulmonary disease, chronic renal disease, and detectable serum troponin levels during hospitalization. They also had a higher blood pressure, LV ejection fraction (LVEF), serum hemoglobin, and serum sodium levels and lower New York Heart Association (NYHA) class, serum creatinine, and blood urea nitrogen levels. Last, these patients were more likely to receive an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker at discharge, less likely to have an implantable cardioverter-defibrillator or CRT, received a lower average daily dose of furosemide, and were less likely to be treated with intravenous inotropes during the hospitalization.

Table 1.   Patient Characteristics

Parameters	All (n=594)	WRF and Cong (n=45)	No WRF/Cong (n=31)	WRF/No Cong (n=253)	No WRF/No Cong (n=265)	P Value
Age, y	69.1±10.75	69.8±9.44	69.8±12.11	70.3±9.56	67.7±11.71	0.0378
Sex, male, n (%)	442 (74)	29 (64)	21 (68)	209 (83)	183 (69)	0.0012
Cause of CVD, n (%) CAD	334 (56)	27 (60)	18 (58)	153 (60)	136 (51)	0.1918
History of diabetes, n (%)	206 (35)	17 (38)	14 (45)	95 (38)	80 (30)	0.1744
History of hypertension, n (%)	316 (53)	24 (53)	18 (58)	140 (55)	134 (51)	0.6835
History of atrial fibrillation, n (%)	215 (36)	21 (47)	12 (39)	99 (39)	83 (31)	0.1175
History of heart failure, n (%)	391 (66)	30 (67)	22 (71)	172 (68)	167 (63)	0.6090
COPD, n (%)	121 (20)	17 (38)	8 (26)	55 (22)	41 (15)	0.0043
Chronic kidney disease, n (%)	207 (35)	22 (49)	13 (42)	110 (43)	62 (23)	<0.0001
NYHA class at admission						
III, n (%)	277 (47)	9 (20)	11 (35)	107 (42)	150 (57)	<0.0001
IV, n (%)	317 (53)	36 (80)	20 (65)	146 (58)	115 (43)	
NYHA class at discharge						
I, n (%)	98 (16)	2 (4)	1 (3)	45 (18)	50 (19)	<0.0001
II, n (%)	350 (59)	12 (27)	18 (58)	152 (60)	168 (63)	
III, n (%)	136 (23)	23 (51)	10 (32)	56 (22)	47 (18)	
IV, n (%)	10 (2)	8 (18)	2 (6)	0 (0)	0 (0)	
Systolic blood pressure, mm Hg						
Admission	128.7±29.97	119.6±30.35	132.6±32.4	130.4±32.23	128.3±27.1	0.1357
Discharge	114.1±18.32	107.8±21.99	113.7±18.33	113.5±18.4	115.8±17.38	0.0474
Heart rate, bpm						
Admission	82±21.28	83.2±17.73	83.3±15.65	84.1±23.2	79.7±20.36	0.1237
Discharge	68.8±10.78	72.5±12.87	70.5±12.02	68.1±9.91	68.6±10.97	0.0712
Weight, kg						
Admission	78.2±16.67	76.6±15.96	78±21.33	78.4±16.05	78.3±16.84	0.9271
Discharge	75.3±15.49	73.8±14.78	76.1±20.36	75±14.6	75.9±15.85	0.8072
Δ from admission to discharge	−2.9±3.61	−2.8±4.53	−1.9±3.26	−3.4±3.72	−2.5±3.3	0.0116
QRS duration, ms	132.2±38.89	134.6±37.91	139.9±37.9	134.6±40.84	128.6±37.09	0.2009
Echocardiography						
LVEF, %	33.3±13.79	31.1±13.97	30.5±12.84	32.7±13.31	34.6±14.25	0.1575
LVEF ≥50 %, n (%)	111 (19)	6 (13)	3 (10)	46 (18)	56 (21)	0.31
Laboratory characteristics						
Serum hemoglobin, mg/dL						
Admission	12.8±1.93	12.3±1.98	13.2±1.74	12.7±1.9	13.1±1.95	0.0132
Discharge	12.6±1.79	11.7±1.74	12.9±1.83	12.4±1.75	12.9±1.76	<0.0001
Serum creatinine, mg/dL						
Admission	1.6±0.82	1.7±0.68	1.7±0.65	1.7±1	1.5±0.64	0.0064
Discharge	1.7±0.79	2.0±0.71	1.5±0.5	1.9±0.91	1.3±0.55	<0.0001
eGFR, mL/min						
Admission	42.8±20.38	36.8±14.05	38±15.15	41.8±23.53	45.4±18.13	0.0142
Discharge	40.5±18.84	29.1±10.91	43.1±16.71	33.1±14.46	49.3±19.85	<0.0001
eGFR, mL/min, median (IQR)						
Admission	47.48 (24.07)	35.7 (18.91)	34.95 (29.59)	38.86 (9.65)	44.87 (24.59)	0.001
Discharge	37.7 (25.44)	25.96 (12.89)	39.53 (25.39)	30.58 (19.39)	46.94 (24.49)	<0.0001
BUN, mg/dL						
Admission	35.3±21.25	42.6±23.41	34.7±18.21	38.1±22.34	31.4±19.37	0.0007
Discharge	38.3±23.46	51.2±32.24	33.2±17.06	45.7±25.92	30.1±15.83	<0.0001
Serum sodium, mEq/L						
Admission	138.7±3.74	137.9±4.63	137.5±4.15	138.7±3.42	138.9±3.79	0.0927
Discharge	139.2±3.68	138.1±3.9	139.4±3.24	139.2±3.71	139.3±3.65	0.2441
Detectable troponin I admission, n (%)	343 (58)	23 (51)	22 (71)	166 (66)	132 (50)	0.0010
NT-proBNP at discharge, No. of patients, pg/mL, median (IQR)	265 2033 (1054–4539)	14 2386 (1576–16152)	35 2760 (1056–5476)	72 1951 (1218–4012)	144 1951 (860–4558)	0.0003

(*Continued*)

Table 1.   Continued

Parameters	All (n=594)	WRF and Cong (n=45)	No WRF/Cong (n=31)	WRF/No Cong (n=253)	No WRF/No Cong (n=265)	P Value
Medications						
ACE inhibitors and/or ARBs, n (%)						
Admission	449 (76)	30 (67)	25 (81)	186 (74)	208 (78)	0.2599
Discharge	458 (77)	28 (62)	24 (77)	187 (74)	219 (83)	0.0085
Aldosterone antagonists, n (%)						
Admission	309 (52)	24 (53)	16 (52)	132 (52)	137 (52)	0.9986
Discharge	402 (68)	32 (71)	22 (71)	175 (69)	173 (66)	0.7514
β-Blockers, n (%)						
Admission	357 (60)	24 (53)	19 (61)	147 (58)	167 (63)	0.7262
Discharge	477 (80)	31 (69)	27 (87)	209 (83)	210 (79)	0.1305
Furosemide, n (%)						
Admission	585 (99)	44 (100)	31 (100)	251 (100)	259 (98)	0.1813
Discharge	564 (95)	45 (100)	31 (100)	241 (95)	247 (93)	0.1239
Furosemide dose, mg/d, mean±SD	108.9±147.49	230.5±202.18	142.7±161.43	124.1±151.84	71.2±113.83	<0.0001
Intravenous therapy during hospitalization						
Nitrates, n (%)	179 (30)	12 (27)	13 (42)	89 (35)	65 (25)	0.0238
Inotropes or dopamine, n (%)	148 (25)	18 (40)	7 (23)	80 (32)	43 (16)	<0.0001

WRF indicates worsening renal function; Cong, congestion; CVD, cardiovascular disease; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; IQR, interquartile range; BUN, blood urea nitrogen; BNP, brain natriuretic peptide; ACE, angiotensin-converting enzyme; ARB, adrenergic receptor binder.

Follow-Up

The median (IQR) duration of the initial hospitalization was 9 (6–15) days. Five patients died on or before the day of discharge from the initial hospitalization. The remaining 594 patients were discharged alive from hospital, 1 of whom was lost to follow-up. Data regarding deaths and hospitalizations were complete for all the other patients. The mean follow-up of these patients was 797±619 days (median [25th, 75th percentiles], 671 [261, 1275] days) from discharge. Within 1 year after discharge, 78 of these patients died (13.1%), 15 (2.5%) received a transplant, and 219 (36.9%) were rehospitalized for AHF.

Determinants of Outcomes

Estimated survival rates in the 4 groups are shown in the Figure (left). The unadjusted risk of death within 1 year of discharge in patients with WRF alone was not higher than in patients with neither WRF nor congestion. However, patients with both WRF and congestion were at significantly higher risk than patients with neither factor. Variables associated with an increased risk of death within 1 year after discharge at multivariable analysis were chronic obstructive pulmonary disease, chronic kidney disease, worse NYHA class, higher heart rate, lower blood pressure, lower body weight, and lower serum sodium (Table 2). After adjustment for these variables, the mortality risks for patients with either WRF alone or residual congestion at discharge alone were not significantly greater than that of patients with neither factor. The increased risk appeared to be driven primarily by the presence of congestion (Figure), and the interaction of congestion with WRF was not statistically significant (P=0.3074). Patients with both
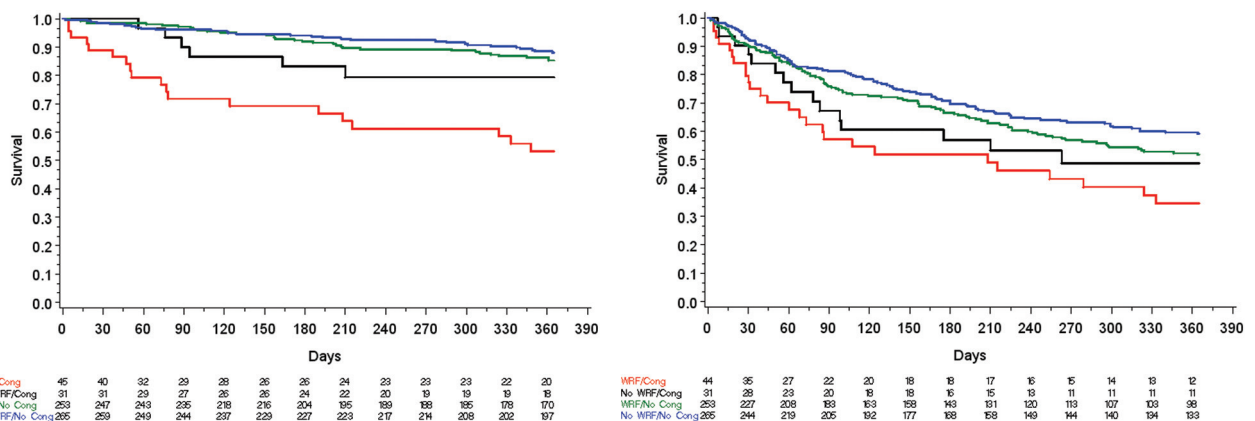

Figure. Outcome for 1-year death or urgent heart transplantation (Tx) (**left**) and for the combined end point of 1-year death, urgent heart transplantation, or heart failure (HF) readmission (**right**) for the patients subdivided on the basis of the development of worsening renal function (WRF) and on the presence of signs of congestion (Cong) at discharge. The number of patients at risk is shown at the bottom.

Table 2. Predictors of Death

Variable	25th, 75th Percentiles	Death or Transplant			
		Univariable HR (95% CI)*	Univariable *P* Value	Multivariable HR (95% CI)*	Multivariable *P* Value
Clinical history					
CKD		1.83 (1.2, 2.78)	0.005	1.79 (1.15, 2.79)	0.0104
COPD		2.04 (1.29, 3.21)	0.0021	1.87 (1.17, 3)	0.0088
Clinical characteristics					
NYHA class, discharge, 4 versus other		7.58 (3.31, 17.39)	<0.0001	5.48 (2.02, 14.89)	0.0009
Systolic blood pressure, admission	110, 140	0.53 (0.41, 0.7)	<0.0001	0.68 (0.52, 0.88)	0.0031
Systolic blood pressure, discharge	100, 125	0.4 (0.29, 0.56)	<0.0001		
Heart rate, discharge	60, 75	1.99 (1.53, 2.59)	<0.0001	1.48 (1.14, 1.92)	0.0032
Weight, discharge	65.6, 82	0.69 (0.53, 0.89)	0.0051	0.72 (0.55, 0.93)	0.0108
Echocardiographic characteristics					
EF, admission	23, 41	0.73 (0.54, 0.98)	0.038		
Laboratory characteristics					
Plasma hemoglobin, discharge	11.2, 14	0.6 (0.42, 0.84)	0.0035		
Serum sodium admission	137, 141	0.6 (0.5, 0.73)	<0.0001		
Serum sodium, discharge†	137, 142	0.48 (0.27, 0.86)	<0.0001	0.69 (0.37, 1.3)	<0.0001
Congestion and WRF					
1: Yes WRF and yes congestion		5.35 (3, 9.55)	<0.0001	2.44 (1.24, 4.81)	0.0097
2: No WRF and yes congestion		1.95 (0.81, 4.7)	0.1364	1.35 (0.52, 3.5)	0.5324
3: Yes WRF and no congestion		1.24 (0.75, 2.03)	0.4037	1.04 (0.62, 1.73)	0.8811
Reference: No WRF and no congestion			Ref		Ref

CKD indicates chronic kidney disease; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; EF, ejection fraction; WRF, worsening renal function.

*Hazard ratios (HR) and 95% confidence intervals (CI) are 75th versus 25th percentiles for continuous variables, or presence versus absence for binary variables.

†Nonlinear relationship with outcome.

WRF and residual congestion at discharge had a hazard of death 3.1 times (95% CI, 1.79–5.44) the hazard for the other patients combined.

Estimated HF readmission-free survival rates in the 4 groups are shown in the Figure (right). The pattern of unadjusted risks was similar to those for mortality, and similar variables were selected as independent determinants of death or HF rehospitalization. Namely, age, a history of chronic renal disease, diabetes, lower systolic blood pressure at both admission and discharge, higher heart rate at discharge, and lower serum hemoglobin levels at discharge were found to be significantly associated with increased risk on multivariable analysis (Table 3). After multivariable adjustment, congestion alone but not WRF alone was associated with poorer outcome. Having WRF in addition to congestion placed a patient at a slightly higher risk, but not significantly (interaction *P*=0.9899). Compared with other patients, patients with both WRF and residual congestion had 1.37 times the hazard (95% CI, 0.89–2.1) for death or HF rehospitalization.

Discussion

The main finding of our study is that WRF alone, defined as an increase in serum creatinine levels ≥0.3 mg/dL from the values measured on admission, differently from a history of chronic kidney disease, had no prognostic value in our patients hospitalized for AHF. However, patients who had WRF and had persistent signs of congestion at the time of discharge had an increased risk of death or of death or rehospitalization, and the association of WRF and persistent congestion was an independent predictor of outcomes, either mortality alone or mortality and HF rehospitalizations.

Thus, our analysis suggests that the prognostic value of changes in serum creatinine levels in patients with AHF is dependent on the presence of congestion. In the absence of congestion, increases in serum creatinine levels do not have prognostic value. In contrast, when serum creatinine levels increase in patients with concomitant congestion, this is associated with poorer outcomes.

As proposed above, the notion that creatinine changes carry significant prognostic value in patients with AHF was mostly driven by retrospective studies in which creatinine measurements were not performed routinely in all patients at multiple time points during admission, such as in the present study, but rather could have been assessed in the sicker patients and in those with a longer duration of hospitalization.[12–15,17] Indeed, this association of serum creatinine increases with outcomes was found to be less prominent in

Table 3. Predictors of Death or HF Rehospitalization

Variable	25th, 75th Percentiles	Death, Transplant, or HF Rehospitalization			
		Univariable HR (95% CI)*	Univariable P Value	Multivariable HR (95% CI)*	Multivariable P Value
Age†	63, 77	0.64 (0.46, 0.88)	0.0134	0.6 (0.43, 0.82)	0.0061
Clinical history					
History of hypertension		0.61 (0.48, 0.78)	0.0001		
Previous HF		1.73 (1.31, 2.29)	0.0001		
CKD		1.69 (1.32, 2.17)	<0.0001	1.43 (1.1, 1.86)	0.0075
Diabetes		1.41 (1.1, 1.81)	0.0075	1.47 (1.12, 1.91)	0.005
Clinical characteristics					
Systolic blood pressure, admission	110, 140	0.65 (0.56, 0.76)	<0.0001	0.75 (0.65, 0.88)	0.0003
Systolic blood pressure, discharge	100, 125	0.57 (0.47, 0.68)	<0.0001	0.68 (0.56, 0.84)	0.0003
Heart rate, admission†	68, 92	1.09 (0.8, 1.5)	0.0079		
Heart rate, discharge	60, 75	1.38 (1.17, 1.63)	0.0002	1.33 (1.12, 1.57)	0.0009
QRS duration	99, 161	1.39 (1.15, 1.68)	0.0008		
NYHA class, discharge, 4 versus other		2.4 (1.13, 5.08)	0.0226		
Echocardiographic characteristics					
EF, admission†	23, 41	0.56 (0.39, 0.81)	0.0016		
Laboratory characteristics					
Plasma hemoglobin, discharge	11.2, 14	0.59 (0.48, 0.72)	<0.0001	0.7 (0.57, 0.87)	0.0011
Serum sodium, admission	137, 141	0.76 (0.68, 0.86)	<0.0001		
Serum sodium, discharge	137, 142	0.77 (0.66, 0.92)	0.0028		
Congestion and WRF					
1: Yes WRF and yes congestion		2.14 (1.39, 3.3)	0.0005	1.39 (0.88, 2.2)	0.1597
2: No WRF and yes congestion		1.49 (0.86, 2.56)	0.152	1.4 (0.81, 2.42)	0.2247
3: Yes WRF and no congestion		1.24 (0.95, 1.62)	0.1182	0.99 (0.74, 1.31)	0.9225
Reference: No WRF and no congestion			Ref		Ref

HF indicates heart failure; CKD, chronic kidney disease; NYHA, New York Heart Association; EF, ejection fraction; WRF, worsening renal function.

*Hazard ratios (HR) and 95% confidence intervals (CI) are 75th versus 25th percentiles for continuous variables or presence versus absence for binary variables.

†Nonlinear relationship with outcome.

studies in which creatinine assessment was done in a serial manner in all patients, independent from their clinical conditions.[6,8,19–21]

The reasons for the variable prognostic value of serum creatinine changes can be found in its multiple determinants, which include local hemodynamic factors influencing the glomerular filtration pressure, in addition to nephron mass. Accordingly, an increase in serum creatinine levels has been often found in patients with relief from congestion. This occurred in 253 (44%) of our patients and was associated with a prognosis similar to that of the patients with no WRF and no congestion. Our patients with WRF and no congestion probably are similar to those who underwent aggressive decongestion for the treatment of decompensated HF in the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial. In this trial, the patients who had hemoconcentration during the hospitalization, used as an index of enhanced diuretic treatment, received higher doses of loop diuretics, lost more weight, and had greater reductions in filling pressures

(P<0.05 for all). These patients had an increased risk of WRF (HR, 5.3; P<0.001) but also a lower 180-day mortality.[24]

A similar mechanism probably was the cause of WRF, defined on the basis of increased serum creatinine levels, in recent intervention trials. Enhanced diuresis with either rolofylline administration or high-dose furosemide administration were associated in the PROTECT (Placebo-controlled Randomized study of the selective A(1) adenosine receptor antagonist rolofylline for patients hospitalized with acute heart failure and volume Overload to assess Treatment Effect on Congestion and renal function) and the DOSE (Diuretic Optimization Strategies Evaluation) trials, respectively, with a slightly greater rate of episodes of WRF, though with better dyspnea relief and better short-term outcomes.[25–27] Similarly, serum creatinine bumps were shown with ultrafiltration in a randomized trial in which this procedure was associated with greater fluid removal and a lower rehospitalization rate.[28] In these cases, serum creatinine increases probably are secondary to arterial underfilling and decreased renal perfusion pressure caused by enhanced diuresis and/or earlier initiation

or uptitration of angiotensin-converting enzyme inhibitors or adrenergic receptor binders (so-called "vasomotor nephropathy").[2,4,29] These changes in serum creatinine levels are usually transient and not associated with permanent renal damage and poor prognosis.

On the other hand, WRF may also be an expression of a more severe hemodynamic impairment and insufficient fluid removal in patients with persistent fluid overload. Namely, low cardiac output and increased central venous pressure and renal vein pressure may cause a reduction in the glomerular filtration pressure, WRF, and resistance to furosemide administration.[30–32] This was the likely mechanism of the increased risk of death and of death or HF rehospitalizations associated with WRF and persistent congestion in our patients.

If confirmed, these findings suggest that changes in serum creatinine are not a reliable tool to detect new or WRF in patients with AHF. This should encourage the search for novel markers in the urine or blood to detect acute renal injury. Some new markers (ie, markers of tubular damage, cystatin-C) have been already tested also in patients with AHF and have generally provided better prognostic information than traditional markers of renal function[33–37] However, more research in this area still must be undertaken.

Our study confirms the ominous prognostic significance of the persistence of signs of congestion at the time of discharge in patients admitted for AHF. Persistent congestion was associated with an increased rate of death or HF rehospitalization and, when associated with WRF, with increased mortality as well. These data are consistent with previous studies and indicate the limitations of current treatment of AHF.[4,26,38,39]

Limitations

The current study represents an analysis of a cohort of consecutive patients admitted for AHF and evaluated and treated by the investigators. This may have introduced a selection bias. Patients dying very early after admission may have not been included into the study, and this may explain the relatively low in-hospital mortality of our patients. On the other hand, the present study is focused on the relationship between in-hospital changes in serum creatinine levels and postdischarge outcomes of the patients rather than in-hospital mortality. Again, because of the characteristics of our patients, the present study has included mostly patients with systolic HF. The results should be therefore interpreted with caution until confirmed in larger less selective prospective cohorts.

Another limitation of the study is that baseline, except in a limited sample of patients, and serial biomarker levels were not measured in this study. Plasma levels of natriuretic peptides are related to myocardial wall stress and have a greater accuracy than clinical signs for the diagnosis of congestion. Only clinical signs were used in our study to diagnose congestion. The diagnostic value of such assessment is increased when multiple signs are assessed, as in our study. However, the diagnosis based solely on clinical signs is less accurate compared when biomarkers and/or dynamic maneuvers are used.[38] In addition, the use of other biomarkers[33–37] and/or of their serial changes during hospitalization[15,36,40] might have yielded a better prognostic assessment, although this is not generally done in everyday clinical practice, yet.

Conclusions

In patients with AHF, serum creatinine changes during admission are associated with adverse outcome only in the presence of congestion. Persistence of congestion during the hospitalization is the most important prognostic factor and WRF has a clinical significance only when occurring in patients with persistent fluid overload. In patients without congestion, serum creatinine changes are potentially the result of intensified therapy with diuretics and angiotensin-converting enzyme inhibitors/adrenergic angiotensin receptor blockers and not markers of worsening HF or kidney function. Better markers of kidney injury should be explored to detect worsening kidney function or HF in patients with AHF.

Disclosures

References

1. Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, Konstam MA, Mancini DM, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation.* 2009;119:1977–2016.

2. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Strömberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K; ESC Committee for Practice Guidelines (CPG). ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur J Heart Fail.* 2008;10:933–989.

3. Metra M, Brutsaert D, Dei Cas L, Gheorghiade M. Acute heart failure: epidemiology, classification and pathophysiology. In: Tubaro M, Danchin N, Filippatos G, Goldstein P, Vranckx P, Zagher D, eds. *The ESC Textbook of Intensive and Acute Cardiac Care.* Oxford/New York: Oxford University Press; 2011:479–490.

4. Gheorghiade M, Pang PS. Acute heart failure syndromes. *J Am Coll Cardiol.* 2009;53:557–573.

5. McClellan WM, Flanders WD, Langston RD, Jurkovitz C, Presley R. Anemia and renal insufficiency are independent risk factors for death among patients with congestive heart failure admitted to community hospitals: a population-based study. *J Am Soc Nephrol.* 2002;13:1928–1936.

6. Nohria A, Hasselblad V, Stebbins A, Pauly DF, Fonarow GC, Shah M, Yancy CW, Califf RM, Stevenson LW, Hill JA. Cardiorenal interactions: insights from the ESCAPE trial. *J Am Coll Cardiol.* 2008;51:1268–1274.

7. Heywood JT, Fonarow GC, Costanzo MR, Mathur VS, Wigneswaran JR, Wynne J; ADHERE Scientific Advisory Committee and Investigators. High prevalence of renal dysfunction and its impact on

outcome in 118,465 patients hospitalized with acute decompensated heart failure: a report from the ADHERE database. *J Card Fail.* 2007;13:422–430.

8. Klein L, Massie BM, Leimberger JD, O'Connor CM, Piña IL, Adams KF Jr, Califf RM, Gheorghiade M; OPTIME-CHF Investigators. Admission or changes in renal function during hospitalization for worsening heart failure predict postdischarge survival: results from the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF). *Circ Heart Fail.* 2008;1:25–33.

9. Harjola VP, Follath F, Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Hochadel M, Komajda M, Lopez-Sendon JL, Ponikowski P, Tavazzi L. Characteristics, outcomes, and predictors of mortality at 3 months and 1 year in patients hospitalized for acute heart failure. *Eur J Heart Fail.* 2010;12:239–248.

10. Butler J, Chirovsky D, Phatak H, McNeill A, Cody R. Renal function, health outcomes, and resource utilization in acute heart failure: a systematic review. *Circ Heart Fail.* 2010;3:726–745.

11. Gottlieb SS, Abraham W, Butler J, Forman DE, Loh E, Massie BM, O'Connor CM, Rich MW, Stevenson LW, Young J, Krumholz HM. The prognostic importance of different definitions of worsening renal function in congestive heart failure. *J Card Fail.* 2002;8:136–141.

12. Krumholz HM, Chen YT, Vaccarino V, Wang Y, Radford MJ, Bradford WD, Horwitz RI. Correlates and impact on outcomes of worsening renal function in patients ≥65 years of age with heart failure. *Am J Cardiol.* 2000;85:1110–1113.

13. Forman DE, Butler J, Wang Y, Abraham WT, O'Connor CM, Gottlieb SS, Loh E, Massie BM, Rich MW, Stevenson LW, Young JB, Krumholz HM. Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. *J Am Coll Cardiol.* 2004;43:61–67.

14. Butler J, Forman DE, Abraham WT, Gottlieb SS, Loh E, Massie BM, O'Connor CM, Rich MW, Stevenson LW, Wang Y, Young JB, Krumholz HM. Relationship between heart failure treatment and development of worsening renal function among hospitalized patients. *Am Heart J.* 2004; 147:331–338.

15. Metra M, Nodari S, Parrinello G, Bordonali T, Bugatti S, Danesi R, Fontanella B, Lombardi C, Milani P, Verzura G, Cotter G, Dittrich H, Massie BM, Dei CL. Worsening renal function in patients hospitalized for acute heart failure: clinical implications and prognostic significance. *Eur J Heart Fail.* 2008;10:188–195.

16. Damman K, Navis G, Voors AA, Asselbergs FW, Smilde TD, Cleland JG, van Veldhuisen DJ, Hillege HL. Worsening renal function and prognosis in heart failure: systematic review and meta-analysis. *J Card Fail.* 2007;13:599–608.

17. Breidthardt T, Socrates T, Noveanu M, Klima T, Heinisch C, Reichlin T, Potocki M, Nowak A, Tschung C, Arenja N, Bingisser R, Mueller C. Effect and clinical prediction of worsening renal function in acute decompensated heart failure. *Am J Cardiol.* 2011;107:730–735.

18. Ruggenenti P, Remuzzi G. Worsening kidney function in decompensated heart failure: treat the heart, don't mind the kidney. *Eur Heart J.* 2011; 32:2476–2478.

19. Cowie MR, Komajda M, Murray-Thomas T, Underwood J, Ticho B. Prevalence and impact of worsening renal function in patients hospitalized with decompensated heart failure: results of the prospective outcomes study in heart failure (POSH). *Eur Heart J.* 2006;27:1216–1222.

20. Testani JM, McCauley BD, Chen J, Shumski M, Shannon RP. Worsening renal function defined as an absolute increase in serum creatinine is a biased metric for the study of cardio-renal interactions. *Cardiology.* 2010;116:206–212.

21. Lanfear DE, Peterson EL, Campbell J, Phatak H, Wu D, Wells K, Spertus JA, Williams LK. Relation of worsened renal function during hospitalization for heart failure to long-term outcomes and rehospitalization. *Am J Cardiol.* 2011;107:74–78.

22. Smilde TD, van Veldhuisen DJ, Navis G, Voors AA, Hillege HL. Drawbacks and prognostic value of formulas estimating renal function in patients with chronic heart failure and systolic dysfunction. *Circulation.* 2006;114:1572–1580.

23. Levey AS, de Jong PE, Coresh J, Nahas ME, Astor BC, Matsushita K, Gansevoort RT, Kasiske BL, Eckardt KU. The definition, classification and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. *Kidney Int.* 2011;80:17–28.

24. Testani JM, Chen J, McCauley BD, Kimmel SE, Shannon RP. Potential effects of aggressive decongestion during the treatment of decompensated

heart failure on renal function and survival. *Circulation.* 2010;122:265–272.

25. Massie BM, O'Connor CM, Metra M, Ponikowski P, Teerlink JR, Cotter G, Weatherley BD, Cleland JG, Givertz MM, Voors A, DeLucca P, Mansoor GA, Salerno CM, Bloomfield DM, Dittrich HC; PROTECT Investigators and Committees. Rolofylline, an adenosine A1-receptor antagonist, in acute heart failure. *N Engl J Med.* 2010; 363:1419–1428.

26. Metra M, O'Connor CM, Davison BA, Cleland JG, Ponikowski P, Teerlink JR, Voors AA, Givertz MM, Mansoor GA, Bloomfield DM, Jia G, Delucca P, Massie B, Dittrich H, Cotter G. Early dyspnoea relief in acute heart failure: prevalence, association with mortality, and effect of rolofylline in the PROTECT Study. *Eur Heart J.* 2011;32:1519–1534.

27. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, LeWinter MM, Deswal A, Rouleau JL, Ofili EO, Anstrom KJ, Hernandez AF, McNulty SE, Velazquez EJ, Kfoury AG, Chen HH, Givertz MM, Semigran MJ, Bart BA, Mascette AM, Braunwald E, O'Connor CM; NHLBI Heart Failure Clinical Research Network. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med.* 2011;364:797–805.

28. Costanzo MR, Guglin ME, Saltzberg MT, Jessup ML, Bart BA, Teerlink JR, Jaski BE, Fang JC, Feller ED, Haas GJ, Anderson AS, Schollmeyer MP, Sobotka PA; UNLOAD Trial Investigators. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J Am Coll Cardiol.* 2007;49:675–683.

29. Schrier RW. Blood urea nitrogen and serum creatinine: not married in heart failure. *Circ Heart Fail.* 2008;1:2–5.

30. Damman K, van Deursen VM, Navis G, Voors AA, van Veldhuisen DJ, Hillege HL. Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease. *J Am Coll Cardiol.* 2009;53:582–588.

31. Mullens W, Abrahams Z, Skouri HN, Francis GS, Taylor DO, Starling RC, Paganini E, Tang WH. Elevated intra-abdominal pressure in acute decompensated heart failure: a potential contributor to worsening renal function? *J Am Coll Cardiol.* 2008;51:300–306.

32. Mullens W, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, Young JB, Tang WH. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. *J Am Coll Cardiol.* 2009;53:589–596.

33. Damman K, van Veldhuisen DJ, Navis G, Voors AA, Hillege HL. Urinary neutrophil gelatinase associated lipocalin (NGAL), a marker of tubular damage, is increased in patients with chronic heart failure. *Eur J Heart Fail.* 2008;10:997–1000.

34. Damman K, Van Veldhuisen DJ, Navis G, Vaidya VS, Smilde TD, Westenbrink BD, Bonventre JV, Voors AA, Hillege HL. Tubular damage in chronic systolic heart failure is associated with reduced survival independent of glomerular filtration rate. *Heart.* 2010;96:1297–1302.

35. Aghel A, Shrestha K, Mullens W, Borowski A, Tang WH. Serum neutrophil gelatinase-associated lipocalin (NGAL) in predicting worsening renal function in acute decompensated heart failure. *J Card Fail.* 2010; 16:49–54.

36. Lassus JP, Nieminen MS, Peuhkurinen K, Pulkki K, Siirilä-Waris K, Sund R, Harjola VP; FINN-AKVA study group. Markers of renal function and acute kidney injury in acute heart failure: definitions and impact on outcomes of the cardiorenal syndrome. *Eur Heart J.* 2010;31:2791–2798.

37. Lassus J, Harjola VP. Cystatin C: a step forward in assessing kidney function and cardiovascular risk. *Heart Fail Rev.* March 23, 2011 [Epub ahead of print].

38. Gheorghiade M, Follath F, Ponikowski P, Barsuk JH, Blair JE, Cleland JG, Dickstein K, Drazner MH, Fonarow GC, Jaarsma T, Jondeau G, Sendon JL, Mebazaa A, Metra M, Nieminen M, Pang PS, Seferovic P, Stevenson LW, van Veldhuisen DJ, Zannad F, Anker SD, Rhodes A, McMurray JJ, Filippatos G; European Society of Cardiology; European Society of Intensive Care Medicine. Assessing and grading congestion in acute heart failure: a scientific statement from the acute heart failure committee of the Heart Failure Association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine. *Eur J Heart Fail.* 2010;12:423–433.

39. Metra M, Cleland JG, Weatherley BD, Dittrich HC, Givertz MM, Massie BM, O'Connor CM, Ponikowski P, Teerlink JR, Voors AA, Cotter G. Dyspnoea in patients with acute heart failure: an analysis of

its clinical course, determinants, and relationship to 60-day outcomes in the PROTECT pilot study. *Eur J Heart Fail*. 2010;12:499–507.

40. O'Connor CM, Fiuzat M, Lombardi C, Fujita K, Jia G, Davison BA, Cleland J, Bloomfield D, Dittrich HC, Delucca P, Givertz MM, Mansoor G, Ponikowski P, Teerlink JR, Voors AA, Massie BM, Cotter G, Metra M. Impact of serial troponin release on outcomes in patients with acute heart failure: analysis from the PROTECT Pilot Study. *Circ Heart Fail*. 2011;4:724–732.

CLINICAL PERSPECTIVE

An increase in serum creatinine, generally defined as worsening renal function (WRF), is considered an ominous prognostic sign in patients with heart failure (HF). However, an increase in serum creatinine may be caused by a relative dehydration secondary to overdiuresis. Thus, the prognostic significance of WRF may depend on the patient's volume status. To ascertain this, we measured serum creatinine levels on a daily basis during hospitalization and assessed the persistence of signs of congestion at discharge in 599 consecutive patients admitted at our institute for acute HF. Patients with WRF and no congestion had similar outcomes compared with those with no WRF and no congestion, whereas the risk of death or of death or HF readmission was increased in the patients with persistent congestion alone and in those with both WRF and congestion. Our data show that WRF has an additive prognostic value only when it occurs in patients with persistent signs of congestion. Accordingly, the serum creatinine changes occurring in the absence of congestion should not influence treatment of HF, hospitalization length, and/or be target of HF treatment.