Clinical Impact of Renal Dysfunction in Heart Failure

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Renal impairment in heart failure (HF) patients has been increasingly recognized as an independent risk factor for morbidity and mortality. In the most recent European and American guidelines for HF management, renal dysfunction was considered an index of poor prognosis independent of the presence of other traditionally investigated risk factors. Different mechanisms appear to be implicated in worsening renal function in patients with acute decompensated HF (ADHF) in contrast to chronic HF. In patients with acute ADHF, renal impairment has been attributed to renal hypoperfusion due to reduced cardiac output and decreased systemic blood pressure. In these patients, neurohormonal activation of the renin-angiotensin and sympathetic nervous systems plays a key role. In chronic and clinically stable HF, other mechanisms, including microvascular damage, oxidative stress, inflammation, and fibrosis, lead to a reduced number of functioning nephrons. Differentiating transient functional changes in renal filtration and acute renal tubular injury with loss of functioning nephrons is a critical step in understanding cardiorenal syndromes and selection of patients for novel therapeutic approaches.
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Heart failure (HF) is the leading cause of hospital admissions in the elderly. In addition to its high prevalence, hospitalization for acute decompensated HF (ADHF) is associated with high rates of morbidity and mortality. The clinical presentation depends on the hemodynamic status and organ perfusion, as well as neurohormonal or toxic renal damage.[1]

Acute kidney injury (AKI) has become increasingly recognized as an independent risk factor for morbidity and mortality. In most circumstances, AKI occurs on top of chronic kidney disease (CKD); this combination acts as an

independent predictor for myocardial infarction (MI), stroke, and cardiac death. It is well known that the progression of renal impairment leads to an increased risk of cardiovascular mortality that cannot be fully explained by conventional risk factors or older age.[2]

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In recent European and American guidelines for HF, the development of renal dysfunction was considered an index of poor prognosis.[3,4] However, in most randomized controlled clinical trials conducted in HF, patients, those with CKD tend to be excluded despite increasing recognition of the prevalence and risks associated with this condition. There are many reasons to recognize renal function in HF: the well-known clinical impact of CKD in common cardiovascular diseases, the high prevalence of this condition in HF, and the need to understand the relative benefits and risks of different therapies for this condition.

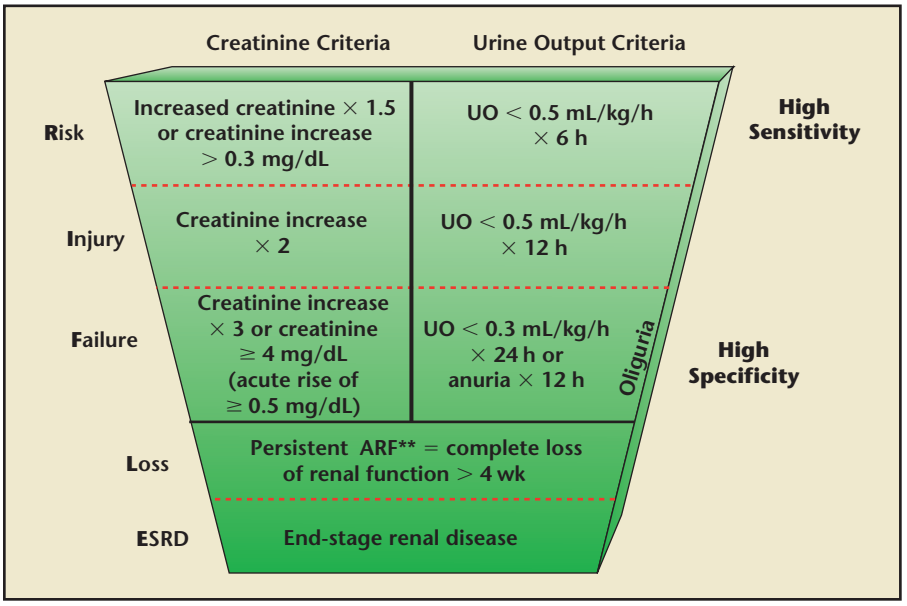
Many studies reported only baseline serum creatinine; however, with contemporary databases that include other demographic data such as age, sex, and weight, the creatinine clearance (CrCl) or estimated glomerular filtration rate (eGFR) could be generated. Recently, the term "worsening renal function" (WRF) has been used to describe the acute and subacute changes that occur to kidney function following episodes of ADHF. For these reasons, it appears mandatory to establish a consensus on the definition and classification for AKI in clinical practice and in future studies enrolling HF patients. This would permit a better standardization in evaluating its incidence, temporal profile, and outcome across future epidemiologic investigations. On the basis of these criteria, we herein describe the prevalence and the clinical impact of AKI in recent clinical trials in the setting of acute and chronic HF.

Renal Dysfunction in ADHF

Data from several sources demonstrate that approximately 20% to 40% of patients with ADHF develop renal impairment, defined on the basis of RIFLE/AKIN (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease/Acute Kidney Injury) criteria (Figure 1).[5,6] The broad range in the reported incidence is largely attributable to the variability in the definition of WRF, differences in the observed time-at-risk, and heterogeneity of study populations.[7,8]

In the Prospective Outcomes Study in Heart Failure (POSH) study, Cowie and colleagues[9] prospectively enrolled 248 patients with ADHF (ejection fraction [EF] < 40% and dyspnea) across eight European countries (mean age 68 years, 74% men). WRF was defined as an increase in serum creatinine > 26 mmol/L from time of admission. The 6-month follow-up was completed in 95% of patients. Nearly one-third of patients (29%) developed WRF during hospitalization. The risk profile of this subgroup was characterized by a major prevalence of increased serum creatinine levels on admission, pulmonary edema, and a history of atrial fibrillation. Although the 30-day mortality and up to 6-month mortality of WRF patients was not significantly increased, the length of hospital stay was 2 days longer. This was not confirmed in patients admitted for the first time for HF with preserved left ventricular (LV) systolic function; Rusinaru and associates[10] demonstrated that a low baseline eGFR is a potent predictor of long-term mortality. In this work, patients with impaired renal function at baseline who developed WRF during

Figure 1. *RIFLE criteria of acute kidney injury based on creatinine and urine output worsening. ARF, acute renal failure; ESRD, end-stage renal disease; RIFLE, risk, injury, failure, loss, ESRD; UO, urine output.*



hospitalization had a particularly poor prognosis. In contrast to these findings, in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial, in which hemodynamic monitoring by pulmonary artery catheter guidance was obtained in patients with advanced HF, baseline renal impairment showed a higher clinical impact on outcome than WRF, defined as a further creatinine increase of > 0.3 mg/dL. The addition of hemodynamic monitoring to clinical assessment neither prevented WRF nor improved renal function after discharge.[11] In the Acute Decompensated Heart Failure National Registry (ADHERE), 30% of hospitalized patients with HF had a history of CKD and 20% had a serum creatinine level > 2 mg/dL in an evaluation of 105,388 hospitalization episodes.[12] Even in this registry, WRF was associated with a more aggressive treatment, increased length of hospital stay, and worsening of in-hospital outcome with increasing severity of renal dysfunction.

In a retrospective analysis of 949 patients from the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF), Klein and coworkers[13] investigated the relationship between admission values and changes in blood urea nitrogen (BUN) and eGFR and the rate of death within 60 days after discharge. Independent of admission values, an increase of > 10 mg/dL in BUN during hospitalization was associated with a worse 60-day survival rate: BUN (per each 5-mg/dL increase) had a hazard ratio (HR) of 1.08 (95% confidence interval [CI], 1.01-1.16). The authors concluded that higher admission and rising BUN concentrations during hospitalization, independent of admission values, are associated with a lower survival rate. Interestingly, BUN on admission and change in BUN during hospitalization were better predictors of poor outcome than eGFR. Similar findings were reported in a large Medicare cohort of patients hospitalized for MI or HF in which a higher BUN on admission was a better predictor of post discharge death than creatinine-based measurements.[14]

This observation could be explained by a higher baroreceptor-mediated nonosmotic arginine vasopressin (AVP) release that determines an increase of urea reabsorption in collecting duct leading to a BUN increase. In fact, in the OPTIME-CHF study, blood pressure (BP) levels were lower in the quartile of patients in which BUN was higher. These patients would be expected to have reduced perfusion and higher baroreceptor-mediated nonosmotic AVP release. Increase in BUN proved to be a marker of a more complex pattern of neurohormonal activation and not merely an index of renal dysfunction[15] (Table 1).

Renal Dysfunction in Chronic HF

Renal impairment is a very common feature in the clinical course of patients affected by HF. The ESCAPE trial showed that 29% of ADHF patients developed WRF during hospitalization in terms of CrCl reduction and that it was associated with impaired outcome during the follow-up period.[16] In a more recent meta-analysis evaluating the prognostic value of WRF in hospitalized HF patients during a 6-month follow-up, the authors revealed a strong association with unfavorable outcome (odds ratio [OR] = 1.62).[17]

Even in less advanced stages of HF, decreased renal function demonstrated an association with increased LV systolic volume and more advanced New York Heart Association (NYHA) class. Again, in the Study of Left Ventricular Dysfunction (SOLVD) trial, patients with moderate renal insufficiency (CrCl < 60 mL/min) experienced greater all-cause mortality, pump failure death, and the composite endpoint of death or hospitalization for worsening HF with a relative risk (RR) of 1.45.[18] In a subsequent analysis of the same study, the authors found that in both the placebo and enalapril groups, older age, diuretic therapy, and diabetes were associated with decreased renal function, whereas β-blocker therapy and higher EF were renoprotective. Older age was associated with an increased risk of developing renal dysfunction in both groups with greater significance in the enalapril-treated group.[19] The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) enrolled patients with severe HF and excluded patients with serum creatinine > 3.4 mg/dL. However, only approximately 10% of patients had a serum creatinine > 2.0 mg/dL.[20]

In the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) Study, Hillege and colleagues[21] found a high incidence of impaired eGFR in the overall study population independent of systolic function, and they showed that eGFR reduction was a stronger predictor for mortality than LV ejection fraction (LVEF) or NYHA class. In the Valsartan in Heart Failure Trial (Val-HeFT), 5010 patients with NYHA class II-IV were randomly assigned to receive valsartan or placebo and were screened for CKD and proteinuria. At baseline, CKD was found in 58% and proteinuria in 8% of patients. Proteinuria was independently associated with mortality (HR 1.28, 95% CI, 1.01-1.62; $P = .05$) and first morbid event (HR 1.28, 95% CI, 1.06-1.55; $P = .01$). However, the increased risk of death

Table 1
Trials in Acute and Chronic Heart Failure Evaluating Renal Function With Cutoff Definition

Study	Population (n)	Study Type	Follow-up	Patients Characteristics	Renal Impairment Definition	Renal Impairment Incidence (%)	WRF Definition	WRF Incidence (%)	Main Results	Renal Outcome
Cowie MR et al[9] (POSH)	299	Prospective	In-hospital, 30 days, 6 months	Hospitalized HF patients	Serum Cr > 26 mmol/L		increase in serum Cr > 0.3 mg/dL	29	Although the mortality of WRF patients was not increased significantly, the length of stay was 2 days longer. The re-hospitalization rate was similar in both groups.	Idem
Rusinaru D et al[10]	358	Prospective	7 years after discharge	First admission to hospital for HF with preserved (≥ 50%) EF	eGFR (MDRD formula) < 60 mL/min/1.73 m^2	53		12	WRF was independently predictive of 7-year overall mortality and CV mortality in patients with low baseline eGFR but not in those with baseline eGFR ≥ 60 mL/min/1.73 m^2	Idem
Nohria A et al[11] (ESCAPE)	433	Prospective	6 months	In-hospital admission for ADHF and severe systolic dysfunction	eGFR (MDRD formula) < 60 mL/min/1.73 m^2		increase in serum Cr > 0.3 mg/dL	29.5	Addition of pulmonary artery catheterization to careful clinical assessment increased anticipated adverse events, but did not affect overall mortality and hospitalization	Baseline and discharge RI, but not WRF, were associated with an increased risk of death or death and rehospitalization
Heywood JT et al[12] (ADHERE Registry)	118,465	Retrospective		In-hospital admission for ADHF	eGFR (MDRD formula) < 89 mL/min/1.73 m^2	91			Hospital mortality increased from 1.9% for patients with normal renal function to 7.6% and 6.5% for patients with severe dysfunction and kidney failure, respectively	Idem
Klein L et al[13] (OPTIME-CHF)	949	Retrospective		In-hospital admission for ADHF and severe systolic dysfunction	eGFR (MDRD formula) and BUN		eGFR decrease > 25% or BUN increase > 25%	12 using eGFR, 39 using BUN	The milrinone and placebo groups did not differ significantly in in-hospital mortality, 60-day mortality, or the composite incidence of death or readmission	Independently of admission values, an increase of > 10 mg/dL in BUN was associated with worse 60-day survival rate

(*Continued*)

Table 1
Trials in Acute and Chronic Heart Failure Evaluating Renal Function With Cutoff Definition (*Continued*)

Study	Population (n)	Study Type	Follow-up	Patients Characteristics	Renal Impairment Definition	Renal Impairment Incidence (%)	WRF Definition	WRF Incidence (%)	Main Results	Renal Outcome
Knight EL et al[19] (SOLVD)	6758	Retrospective	974 days (enalapril), 967 days (placebo)	Asymptomatic and symptomatic CHF outpatients with left ventricular systolic dysfunction (EF < 30%)	eGFR (Cockcroft-Gault equation) < 60 mL/min		Rise in serum Cr ≥ 0.5 mg/dL from baseline	31	Enalapril use caused a 33% increase in the risk of decreased renal function in patients with CHF; diuretic use and advanced age increased this risk; diabetes was associated with an increased risk of renal impairment in all patients with CHF, but this risk was reduced in the enalapril group; β-blocker therapy and higher EF were renoprotective in all patients regardless of therapy	Idem
Hillege HL et al[21] (CHARM)	2680	Prospective	4 years	Patients with chronic HF with and without LV dysfunction	eGFR (MDRD formula) < 60 mL/min/1.73 m^2	42.6% for CHARM-Alternative, 33.0% for CHARM-Added, 34.7% for CHARM-Preserved			Candesartan was generally well tolerated and significantly reduced CV deaths and hospital admissions for HF; EF or treatment at baseline did not alter these effects	The risk for CV death or hospitalization for worsening CHF as well as the risk for all-cause mortality increased significantly below an eGFR of 60 mL/min per 1.73 m^2
Anand IS et al[22] (Val-HeFT)	5010	Clinical trial	The overall mean duration of follow-up was 23 months (range, 0-38 mo)	Patients with stable, symptomatic HF (NYHA class II-IV), receiving recommended HF therapy, LVEF < 40%	eGFR (MDRD formula) < 60 mL/min/1.73 m^2 and/or dipstick positive proteinuria	58% (renal impairment), 8% (dipstick-positive proteinuria)			Valsartan caused sustained reduction in BNP and attenuated the increase in NE over the course of the study; these neurohormonal effects of valsartan are consistent with the clinical benefits	Dipstick-positive proteinuria was independently associated with mortality and first morbid event; the increased risk of death associated with dipstick-positive proteinuria was similar for those with and without CKD; valsartan reduced the eGFR by the same amount in patients with and without CKD and reduced the risk of the first morbid event in patients with CKD

Table 1
Trials in Acute and Chronic Heart Failure Evaluating Renal Function With Cutoff Definition (*Continued*)

Study	Population (n)	Study Type	Follow-up	Patients Characteristics	Renal Impairment Definition	Renal Impairment Incidence (%)	WRF Definition	WRF Incidence (%)	Main Results	Renal Outcome
Saxon LA et al[24] (COMPANION)	1520	Clinical trial	> 4 years	HF outpatients with NYHA class III-IV with ischemic or dilated cardiomyopathy	eGFR < 40 mL/min	25			The CRT-defibrillator device reduced the risk of sudden death by 56% compared with drug therapy; CRT therapy was not associated with sudden death risk reduction	eGFR < 40 mL/min was an independent predictor of sudden death
Goldenberg I et al[25] (MADIT II)	1232	Retrospective analysis		Patients with documented MI and EF < 30%	eGFR (MDRD formula) < 60 mL/min/1.73 m^2	38			ICD therapy has been shown to be associated with a significant reduction in the risk of SCD in patients with ischemic LV dysfunction	Significant increase in all-cause mortality and SCD with decline of renal function; defibrillator therapy was associated with a significant survival benefit among patients with mild to moderate or no renal disease, but no benefit was shown among patients with more advanced renal dysfunction

ADHERE, Acute Decompensated Heart Failure National Registry; ADHF, acute decompensated heart failure; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; CHARM, Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity; CHF, congestive heart failure; CKD, chronic kidney disease; COMPANION, Comparison of Medical Therapy Pacing and Defibrillation in Heart Failure; Cr, creatinine; CRT, cardiac resynchronization therapy; CV, cardiovascular; EF, ejection fraction; eGFR, estimated glomerular filtration rate; ESCAPE, Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness; HF, heart failure; ICD, implantable cardioverter defibrillator; LV, left ventricular; MADIT, Multicenter Automatic Defibrillator Implantation Trial; MDRD, Modification of Diet in Renal Disease; MI, myocardial infarction; NE, norepinephrine; NYHA, New York Heart Association; OPTIME-CHF, Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure; POSH, Prospective Outcomes Study in Heart Failure; RI, renal insufficiency; SCD, sudden cardiac death; SOLVD, Study of Left Ventricular Dysfunction; Val-HeFT, Valsartan in Heart Failure Trial; WRF, worsening renal function.

associated with proteinuria was similar for patients both with and without CKD (HR 1.26, 95% CI, 0.96-1.66 vs HR 1.37, 95% CI, 0.83-2.26; $P = .94$), as well as for first morbid event (HR 1.26, 95% CI, 1.01-1.57 vs HR 1.42, 95% CI, 0.98-2.07; $P = .71$).[22] Therefore, patients with LV dysfunction and CKD have an increased risk of sudden death. This is due to the commonly observed association with coronary artery disease (CAD): the coronary trees of CKD patients often have multiple plaques with diffuse atherosclerosis and severe stenoses. LV hypertrophy together with transient hypotension could produce ischemic episodes. The common elevation in troponin may be a marker of myocardial injury as well as a trigger for ventricular arrhythmia.[23] Data from the Comparison of Medical Therapy Pacing and Defibrillation in Heart Failure trial (COMPANION) confirmed this trend, showing that eGFR $<$ 40 mL/min was an independent predictor of sudden death (OR, 3.2).[24] Similarly, the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II data demonstrated a significant risk increase for sudden death with renal function decrease. Defibrillator therapy was associated with a significant survival benefit among the study patients with mild to moderate renal disease.[25]

A recent systematic meta-analysis demonstrated that 29% of HF patients had moderate to severe CKD, and during a 1-year follow-up, mortality occurred in 38% and 51% of patients who presented mild or severe CKD, respectively, as compared with patients with normal renal function. Renal impairment showed an incremental and linear increase in mortality risk with 15% increased risk for each 0.5-mg/dL creatinine increase.[26] In a retrospective analysis of data from 1129 patients, a discharge serum creatinine level $>$ 2.5 mg/dL was the most powerful independent predictor of all-cause readmission (OR, 1.72).[27] In a recent study, Tsagalis and associates[28] investigated the prevalence of HF and renal dysfunction (defined as eGFR $<$ 60 mL/min/1.73 m^2) in patients with acute stroke: HF and CKD were both independent predictors of mortality in a 10-year follow-up and age, history of transient ischemic attacks, and combined HF and CKD were independent predictors of new cardiovascular events (Table 1).[28]

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The Meaning of Worsening Renal Function

When creatinine levels begin to rise with treatment of ADHF, it is unclear which patients are having transient reductions in renal blood flow and therefore function changes in renal filtration, as opposed to acute renal tubular injury, which goes through a classic period of injury, stabilization, and recovery. As reported in the meta-analysis of Damman and coworkers,[17] a rise in serum creatinine in patients with higher basal levels has a different meaning when compared with a similar rise in patients with normal basal values. The authors concluded that the Modification of Diet in Renal Disease (MDRD) formula is the most accurate to calculate eGFR in patients with HF and that mortality starts to significantly increase with an eGFR decrease of $>$ 9 mL/min/1.73 m^2. There are many studies that have validated estimated CrCl (Cockcroft-Gault) and eGFR from plasma creatinine concentrations (MDRD). Several methodological problems exist: the selection of study population, the analysis method, the calibration of the creatinine measurement, the different eGFR reference methods used, and the choice of the statistical methods used for the comparison. MDRD is considered less biased and is the recommended creatinine-based formula for the follow-up of patients with CKD.[29] However, a more accurate estimation of individual renal function profile cannot be obtained only with creatinine-based eGFR. The evaluation of serum levels of cystatin C has been recently proposed as a reliable marker of eGFR. Cystatin C is a cysteine proteinase filtered by the glomerulus and metabolized by proximal tubules without being secreted into tubules. Thus, its clearance could be used, as well as the CrCl, as a reliable index of GFR. Cystatin C clearance is not affected by age, sex, or muscle mass, which traditionally limit creatinine-based GFR estimations, such as the Cockcroft-Gault or MDRD formulas.[30] In a study by Tidman and associates,[31] several analytical methods for both creatinine and cystatin C GFR estimations were compared using plasma clearance of iohexol as the referent method. The authors concluded that both creatinine and cystatin C estimates have a similar accuracy. Thus, it can be expected that combining GFR estimates from both these analyses should give a more accurate stratification of renal dysfunction. In fact, creatinine has a variable tubular secretion and reabsorption, but a small nonrenal clearance, whereas cystatin C has a greater and more variable nonrenal clearance.

The sources of error for estimating GFR from cystatin C and creatinine are distinctly different. In patients with a small muscle mass, who have

an abnormal increase of creatinine production, the GFR estimate from cystatin C could be preferred. Several studies suggest the use of albuminuria as a marker of renal dysfunction. Macroalbuminuria (defined as urine albumin:creatinine ratio [UACR] > 300 mg/g) and microalbuminuria (UACR 30-300 mg/g) often precede the renal function deterioration, evidenced by a decline in eGFR, and are associated with an increase of cardiovascular risk in both diabetic and nondiabetic patients. In a recent analysis of the CHARM study,[32] the prevalence of microalbuminuria and macroalbuminuria, and the predictive value of UACR for the primary composite outcome (ie, death from cardiovascular causes or admission for worsening heart failure, and death from any cause) were assessed. Of 2310 patients, 704 (30%), had microalbuminuria, and 257 (11%) had macroalbuminuria. The prevalence of increased UACR was similar in patients with reduced and preserved LVEFs. Patients with an increased UACR were older, had more cardiovascular comorbidity, worse renal function, and a higher prevalence of diabetes mellitus than patients with normoalbuminuria. However, a high prevalence of increased UACR was still noted among patients without diabetes, hypertension, or renal dysfunction.[33] Elevated UACR was associated with an increased risk of the composite outcome and death even after adjustment for other prognostic variables. This finding suggests that even a subclinical deterioration of renal function, assessed by albuminuria estimation, could have a significant negative impact on the outcome of patients with HF.

Several studies have also recently proposed the clinical use of serum neutrophil gelatinase-associated lipocalin (NGAL) levels in patients admitted to the hospital for ADHF to estimate the risk of early WRF. NGAL is produced by the nephron in response to tubular epithelial damage and is considered an early marker for acute renal tubular injury in several clinical settings.[34,35] Recently, in 91 patients admitted to the hospital with ADHF, Aghel and colleagues[36] observed that patients who developed WRF versus those without WRF had significantly higher median admission serum NGAL levels (194 [interquartile range 150-292] ng/mL vs 128 [interquartile range 97-214] ng/mL; $P = .001$). They observed that patients with admission NGAL values ≥ 140 ng/mL had a 7.4-fold increase in risk of developing WRF, with a sensitivity and specificity of the cutoff of 86% and 54%, respectively. At this moment, a consensus to clearly define WRF is lacking (Table 2).

Renal Dysfunction in the Pathogenesis of HF

The mechanisms by which the onset of acute HF or acutely decompensated chronic HF lead to AKI are multiple and complex. The pathophysiology of AKI during ADHF is poorly understood and it likely involves interrelated hemodynamic and neurohormonal mechanisms that could worsen cardiovascular outcomes in these patients. In particular, neurohormonal activation is more intense in patients with acute renal dysfunction and it is associated with altered tubuloglomerular feedback. In addition, recent studies have demonstrated that venous congestion, rather than low cardiac output, is associated with WRF in ADHF.[16] The clinical importance of each mechanism of AKI is likely different from patient to patient (eg, acute cardiogenic shock vs hypertensive pulmonary edema). In acute HF, AKI appears to be more severe in patients with impaired LVEF compared with those with preserved LV function, achieving an incidence > 70% in patients with cardiogenic shock.[37]

In patients with HF and concomitant CKD, other mechanisms have been proposed to explain poor outcomes. These include accelerated hypertension, LV hypertrophy, increased activation of the renin-angiotensin system, reduced renal perfusion, diuretic resistance, and volume overload secondary to difficulties with sodium excretion.[38,39]

Renin-angiotensin-aldosterone system (RAAS) activation is common in patients with chronic HF and leads

Table 2
New Biomarkers for Early Detection of Cardiorenal Syndromes

Biomarker	Associated Injury
KIM-1	Ischemia and nephrotoxins
NGAL (lipocalin)	Ischemia and nephrotoxins
NHE3	Ischemia, prerenal postrenal acute kidney injury
Cytokines (IL-6, 8, 18)	Delayed graft function, inflammatory activity
Troponin T	Myocardial injury, hemodynamic overload
Actin, actin depolymerizing factor	Ischemia and delayed graft function
BNP	Hemodynamic overload, neurohormonal activity
N-terminal pro-BNP	Hemodynamic overload, neurohormonal activity
Cystatin C	Proximal tubule injury

BNP, B-type natriuretic peptide; IL, interleukin; KIM-1, kidney injury molecule-1; NHE3, Na+/H+ exchanger 3; NGAL, Neutrophil gelatinase-associated lipocalin.

to several consequences: renal efferent arteriolar vasoconstriction, increased peritubular capillary oncotic pressure, and reduced peritubular capillary hydrostatic pressure with kidney flow redistribution. Therefore, angiotensin itself causes the proliferation of smooth muscle cells and adventitial fibroblasts in the vascular wall, intrarenal blood vessel thickness, intraglomerular hypertension, glomerulosclerosis, and tubulointerstitial fibrosis.[38] The activation of vasoactive neurohormonal systems, the sympathetic nervous system (SNS), and the RAAS during early stages permits circulatory homeostasis to be maintained. RAAS activation induces direct systemic vasoconstriction and activates other systems (eg, AVP, aldosterone) that contribute to maintaining an adequate intravascular volume. However, the chronic activation of these systems can have deleterious effects on cardiac function and contributes to the progression of HF.[39,40] The activity of the RAAS is central to the maintenance of water and electrolyte balance and blood volume. The enzyme renin is released primarily by the juxtaglomerular cells of the kidney in response to the activity of the SNS, changes in renal perfusion pressure, reduced sodium absorption by the distal renal tubules, or AVP release.[41]

In acute HF, the decrease in renal blood flow caused by progressive HF activates the RAAS. This increase in RAAS activity contributes to systemic vascular resistance. Increased vasoconstriction caused by RAAS activation results in increased LV afterload. This, in turn, increases myocardial demand, LV end-diastolic pressure, pulmonary capillary wedge pressure, and pulmonary congestion, while decreasing cardiac output.[42]

Angiotensin also promotes inflammatory pathways with tumor necrosis factor and interleukin overexpression, tissue remodeling with vascular cell growth and increase of growth factors, endothelial dysfunction by nitric oxide reduction and platelet aggregation, and oxidative stress by induction of reactive oxygen species.[43] Vascular remodeling and fluid overload are also potentiated by the SNS and AVP. The increased intravascular volume induced by AVP-mediated reabsorption of free water results in elevated intracardiac pressure, pulmonary congestion, and edema. Systemic vasoconstriction mediated by angiotensin II increases LV afterload and it can also directly induce cardiac myocyte necrosis and alter the myocardial matrix structure.[44] Counter-regulatory mechanisms consisting in the natriuretic peptides, nitric oxide, and prostaglandins are generally not adequate to maintain cardiac function, systemic perfusion, or sodium balance. The end result of RAAS activation in HF is clinical deterioration and progressive LV dysfunction. It is well documented that the degree of neurohormonal activation is correlated with severity of HF.

RAAS promotes the SNS activity that increases cardiac contractility and heart rate, which in turn increases stroke volume and peripheral vasoconstriction.[45] However, the cardiac work increase leads to an acceleration of the disease progression. The activation of SNS has been attributed to a withdrawal of normal restraining influences and enhancement of excitatory inputs including changes in peripheral baroreceptor and chemoreceptor reflexes—chemical mediators that control the sympathetic outflow. The sympathetic hyperactivity observed in HF is closely related to abnormalities in cardiovascular reflexes: the sympathoinhibitory cardiovascular reflexes are significantly suppressed, whereas the sympathoexcitatory reflexes, including the cardiac sympathetic afferent reflex and the arterial chemoreceptor reflex, are augmented.[40] Sympathetic activation in the setting of impaired systolic function reflects the net balance and interaction between appropriate reflex compensatory responses to impaired systolic function and excitatory stimuli that elicit adrenergic responses in excess of homeostatic requirements. All these changes drive toward an altered cardiac and vascular vasodilating capacity, renal arterial vasoconstriction, and kidney flow redistribution with increased sodium resorption. The cardiac oxygen utilization and vascular resistance increase, β-receptor downregulation and sympathovagal unbalance occur.[46]

If not interrupted, the sympathetic activity will become the principal reason of impairment and mortality in advanced stages of the disease. The physiologic response to HF is the "adrenergic defense," which involves inotropic, chronotropic, and vasoconstrictive reserves.[37]

The hemodynamic consequences result in both fluid retention and sodium reabsorption, with an increase of central venous pressure, which is a key determinant of WRF.[47] These data support the fact that the etiology of cardiorenal syndrome (CRS) in patients with HF is complex, and several factors may be at work in the same patient.[48] Furthermore, the study supports the idea that congestive kidney failure must be considered in addition to congestive heart failure, which is too often considered the only core lesion (Figure 2).[49]

The majority of these traditional and new risk factors are poorly investigated in CRS, and the exact clinical impact is unclear. When WRF was analyzed as a marker of poor outcome in patients with chronic or ADHF, a statistical analysis was adjusted for basal characteristics that may determine WRF in patients with HF (male sex, kidney dysfunction at the time of hospital admission, worsened HF, tachyarrhythmias, and elevated BP at

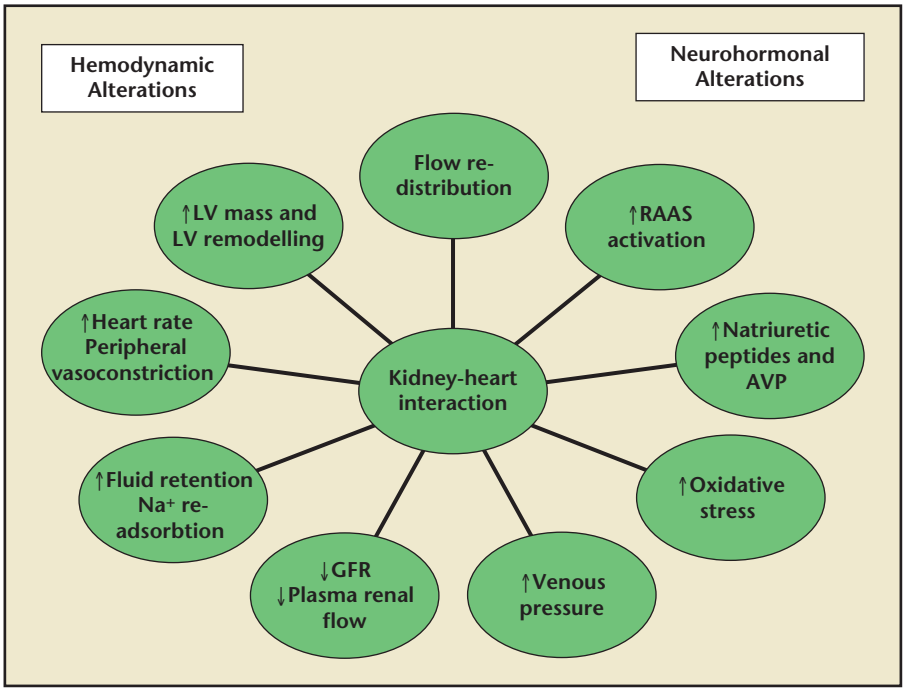

Figure 2. *Pathophysiologic mechanisms of cardiorenal syndrome. On the left, hemodynamic impairment is described; on the right, neurohormonal activation is described. AVP, arginine vasopressin; GFR, glomerular filtration rate; LV, left ventricular; RAAS, renin-angiotensin-aldosterone system.*

hospital admission). In fact, these basal conditions can determine WRF and have also been demonstrated to be predictors of poor outcome in patients with HF, independently of their effect on renal function. Hillege and colleagues,[21] in the CHARM study, demonstrated that the number of comorbidities at baseline increased with decreasing eGFR. In a study by Forman and associates,[26] after adjusting for potential confounding factors including demographics characteristics (age, race), medical history (atrial fibrillation, cerebrovascular accident, HF, diabetes, digoxin use), clinical presentation at admission (orthopnea, hypotension, edema, high respiratory rate, systolic BP $>$ 160 mm Hg), and laboratory examinations (potassium, creatinine, and BUN), the association between WRF and worse clinical outcomes remained significant. The authors proposed a risk score model including four parameters (history of pre-existing HF, diabetes mellitus, admission creatinine of 1.5 mg/dL [132.6 μmol/L], admission systolic BP $>$ 160 mm Hg) that are strongly and independently associated with WRF. This model distinguished the risk of developing WRF ranging from 10% to 53% among different HF patients. On the basis of these data, specific studies aimed to verify the prognostic role of WRF and other risk factors in patients with HF are needed to clarify the relationship between comorbidities and WRF.

Arrhythmias

An independent relationship among renal dysfunction, ventricular tachycardia/fibrillation, and sudden cardiac death (SCD) was shown in several registries among patients with severe renal insufficiency.[50,51] Patients who submitted to hemodialysis showed an incidence of SCD of approximately 25% during a 5-year follow-up period.[52,53] On the basis of the data above, the National Kidney Foundation/American Heart Association (AHA) guidelines have classified renal disease as a cardiovascular disease risk equivalent.[54] This occurs not only in acute settings (ie, CRS 1 and 3), but also in chronic diseases (ie, CRS 2 and 4) in which progressive renal impairment leads to SCD. In this peculiar population, arrhythmic complications must be due to different mechanisms than those studied by the main randomized controlled trials on SCD. Patients with renal insufficiency are subject to unique factors that can both alter the underlying substrate and trigger ventricular arrhythmic events; uremic accumulation, acidemia, and hyperkalemia could all be potential contributing factors for major arrhythmic complications and cardiac arrest. In fact, retrospective analysis demonstrated that up to 71% of dialysis patients who died of SCD had either normal LV function or normal to moderate dysfunction.[55] Echocardiographic studies have reported a high prevalence of cardiac abnormalities in chronic dialysis patients, specifically, LV hypertrophy, systolic or diastolic dysfunction, and ventricular dilatation. These echocardiographic findings have been reported to be strong predictors of cardiac

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mortality, particularly in this population.[56] Therefore, patients with CKD have more frequent CAD involvement and severity; they are all potential risk factors for SCD.

In MADIT II, the authors demonstrated that, despite the fact that the risk of SCD increases with declining renal function, the benefit of implantable cardioverter defibrillator (ICD) therapy appears to be attenuated in patients with advanced renal disease.[25] This is probably due to the selected populations with respect to previous studies enrolling patients with CKD. Second, the trial did not record clinical data regarding the cause and duration of renal dysfunction, and laboratory data were based on CrCl calculated by Cockcroft-Gault equation. CKD is a strong predictor of time to first ICD therapy. This is balanced by higher device complication rates, such as infection, and higher mortality from noncardiovascular causes. Conversely, in another similar study conducted in patients with lesser-degree CKD, it has been well demonstrated that the use of β-blockers was associated with a 39% of RR reduction; however, only 59% of patients are submitted to this treatment.[23]

These data raise a series of questions regarding which patients may deserve ICD therapy with regard to outcome, if all insulin-resistant and HF patients are submitted to the adequate tailored therapy, if all HF and CKD patients have the same arrhythmic risks, and if there is a common clinical behavior apt to prevent or delay this type of complication. Further studies targeted on patients with cardiorenal and renocardiac syndromes could be done to clarify all these aspects.

Therapeutic Implications

Patients with renal disease are more likely to die of cardiovascular disease than progress to end-stage renal disease.[57] Typically, HF patients with creatinine $\geq$ 2.5 mg/dL have been systematically excluded from therapeutic trials and, therefore, optimal pharmacotherapy for patients with HF and CKD remains uncertain. Coca and coworkers[58] reviewed 153 trials to quantify the representation of patients with renal disease in randomized controlled trials for interventions proven efficacious for cardiovascular disease. They revealed that 86 of 153 trials (56%) excluded patients with renal disease and that only in five trials absolute definitions (eg, threshold serum creatinine level) for renal disease were used in the protocols. In most of the remaining cases, the criterion for the exclusion of "renal disease" or an equivalent term was left up to interpretation by the individual site.[58]

The Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure (UNLOAD) trial was a prospective, randomized, multicenter trial evaluating the effect of early ultrafiltration versus intravenous (IV) diuretics in 200 patients hospitalized with HF, mild renal insufficiency, and hypervolemia. Despite similar fluid loss with ultrafiltration and continuous diuretic infusion, at 90 days there were only some significant differences between the two groups in terms of patients rehospitalized for HF (16 of 89 [18%] vs 28 of 87 [32%]; $P = .037$), HF rehospitalization (0.22 of 0.54 vs 0.46 of 0.76; $P = .022$), and rehospitalization days (1.4 of 4.2 vs 3.8 of 8.5; $P = .022$). The only slightly more significant advantage in the ultrafiltration group was in terms of unscheduled office and emergency department visits (14 of 65 [21%] vs 29 of 66 [44%]; $P = .009$).[59] In the most recent AHA guidelines, hemofiltration and dialysis were recommended for patients with serum creatinine $>$ 5 mg/dL to control fluid retention, reduce the risk of uremia, and to continue the traditional treatment methods of HF. In the OPTIME-CHF study,[13] a significant rise in jugular venous pressure was observed as quartile BUN values rose. In this clinical setting, in which volume overload and activation of RAAS are present, hemofiltration therapy—reducing fluid overload—could potentially reduce RAAS activation. The Improve the Use of Evidence-Based Heart Failure Therapy in the Outpatients Setting (IMPROVE HF) study reported that, in patients with HF and LV dysfunction, the severity of concomitant CKD was an independent predictor of adherence to angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) therapy, but not to any of the other guideline recommendations measured in outpatient cardiology practices.[60]

The potential benefit of ACEI/ARB therapy in patients with HF and moderate to severe insulin resistance is still unclear. Masoudi and colleagues[61] reported similar or even increased survival rates for ACEi-treated HF patients with concomitant severe insulin resistance as compared with patients with moderate insulin resistance or normal renal function.[61] In contrast with these findings, other authors[19] didn't observe any potential benefit in terms of mortality rate in patients with ischemic HF and CrCl $<$ 30 mL $\times$ min $\times$ 1.73 m^2 who were treated with ACEI.

With regard to β-blocker therapy, two studies have probed the potential benefit of the β-blocker carvedilol in dialysis patients with dilated cardiomyopathy. Throughout a follow-up of several years, there was greater survival and fewer hospitalizations in the β-blocker–treated group as compared with placebo, suggesting a potential beneficial role for carvedilol in this clinical setting.[62,63]

Recently, a potential beneficial role in patients with ADHF and renal impairment has been proposed for rolofylline, an adenosine A_1 receptor antagonist. The Prophylaxis of Thromboembolism in Critical Care (PROTECT) trial has been designed to investigate its potential role and to individuate an efficacious dose.[64] In 301 patients hospitalized for acute HF with an estimated CrCl of 20 to 80 mL/min and elevated natriuretic peptide levels, within 24 hours from admission, placebo or rolofylline 10, 20, or 30 mg was administered as 4-hour infusions for 3 days in addition to IV-administered loop diuretics. Serum creatinine increased in patients receiving placebo and remained stable or tended to decrease in those receiving rolofylline. After 2 weeks of treatment, a stabilization of the increase in creatinine levels was observed in patients who received rolofylline compared with those who received placebo, and this was directly related to increasing the rolofylline dose ($r = -0.12$; $P = .030$). The authors observed also that treatment with rolofylline 30 mg/d was associated with a trend toward a reduced 60-day mortality or early readmission for cardiovascular or renal cause (HR, 0.55; 95% CI, 0.28-1.04). Tolvaptan, a selective V2-receptor antagonist, was tested as a new drug in patients with ADHF. In the Acute and Chronic Therapeutic Impact of Vasopressin Antagonist in Chronic Heart Failure (ACTIV in CHF) study, a trend toward lower mortality was found in a subgroup of patients with high BUN levels or severe systemic congestion. A post hoc analysis confirmed BUN as a significant predictor of both mortality and the composite endpoint of death or HF hospitalization at 60 days.[65] However, in terms of clinical outcome, these data should be interpreted with caution; these were phase II studies, with a relatively small database and perhaps all factors that could affect the outcome may not have been analyzed and this could have confused the association between BUN levels and the outcome. In the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) study,[66] short- and long-term effects of tolvaptan in patients hospitalized with ADHF and documented evidence of impaired LVEF were investigated. Although in the early phase, a significant clinical improvement (dyspnea, edema, body weight, and serum sodium) was revealed, the long-term outcome trial showed no effect, neither favorable nor unfavorable, on its primary outcome. More targeted studies are needed to improve therapeutic strategies in patients with renal impairment and HF.[49]

Conclusions

HF and CKD are two clinical conditions often associated particularly in certain subtypes of patients with common risk factors and cardiovascular characteristics (ie hypertension, diabetes, older age, high atherosclerotic burden). Renal impairment in HF patients has been recognized as an independent risk factor for morbidity and mortality but, unfortunately, the most important clinical trials in HF tend to exclude patients with CKD. Moreover, CKD and HF may be mutually deleterious by amplifying pathophysiologic mechanisms that lead to a dangerous vicious cycle. Because of several confounding factors, it remains unclear whether WRF specifically contributes to poor outcomes or whether it is merely a marker of advanced cardiac and renal dysfunction. Specific studies evaluating the clinical impact and treatment strategies of WRF in acute and chronic HF are lacking. Thus, the need to better evaluate the association between the two conditions appears mandatory. ■

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Main Points

- Both acute and chronic kidney disease have a significant clinical impact on outcomes in heart failure (HF). A similar trend is reported for patients with primitive kidney disease and HF development.
- There is a need to better understand the pathophysiologic link between the heart and kidney, and to understand the more sensitive and specific laboratory parameters capable of identifying organ damage and potential disease progression.
- Biomarkers may represent a cornerstone in the evaluation of these syndromes and in detecting early organ damage, making prevention of disease progression possible.
- The lack of specific trials in this field demands careful monitoring in titration and balance between renal and cardiac function.

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