CardioRenal Medicine

Cardiorenal Med 2012;2:281–297
DOI: 10.1159/000342487
Published online: October 31, 2012

1664–3828/12/0024–0281$38.00/0
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Review

Comorbid Heart Failure and Renal Impairment: Epidemiology and Management

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Key Words
Heart failure · Renal failure · Cardiorenal syndrome

Abstract
Heart failure mortality is significantly increased in patients with baseline renal impairment and those with underlying heart failure who subsequently develop renal dysfunction. This accelerated progression occurs independent of the cause or grade of renal dysfunction and baseline risk factors. Recent large prospective databases have highlighted the depth of the current problem, while longitudinal population studies support an increasing disease burden. We have extensively reviewed the epidemiological and therapeutic data among these patients. The evidence points to a progression of heart failure early in renal impairment, even in the albuminuric stage. The data also support poor prescription of prognostic therapies. As renal function is the most important prognostic factor in heart failure, it is important to establish the current understanding of the disease burden and the therapeutic implications.

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Introduction

Comorbid heart failure (HF) and renal impairment (RI) is an evolving epidemic faced by an increasing number of medical practitioners. Coronary artery disease invigorated innovation and advancements in cardiac research and delivery of state-of-the-art pharmacological and device therapies. Without a doubt, these patients are enjoying a better standard of living and life expectancy. Since Lindner et al. [1] first described the association between cardiovascular diseases (CVD) in patients with end-stage renal disease (ESRD), we have come to realise this association is more complex. For example, the permutations relate to the primary organ involved, the severity of the organ involvement, the degree of organ cross talk and compensatory feedback, temporal factors and a host of other factors. Consequently, we often see these patients undertreated as physicians do not know where to start or fear that treating the worse organ may provoke the progression of the other. Quite strikingly, the number of patients at risk also continues to accelerate while there has been negligible progress in improving outcomes. The increased complexity of this syndrome may be a contributing factor in the slow progress. While we await novel diagnostics and therapeutics, the interim should focus on advancing the understanding of the cardiorenal pathophysiology and the interpretation of conventional biochemistry. We refer the reader to several recent reviews in the area that have addressed this issue [2–7]. This review focuses on updates on cardiorenal epidemiology and therapeutics, with special emphasis on both cardiorenal and renocardiac perspectives. Please note that in this article, we use chronic renal insufficiency (CRI) and reduced estimated glomerular filtration rate (eGFR) to imply renal functional limitations. We use chronic kidney disease (CKD), sparingly, to encompass the entire spectrum of renal diseases with or without functional limitations.

Epidemiological Association between CRI and HF

The last several years have shed significant insights into the cardiorenal epidemiology with data from three large registries [8–12]. On the therapeutic side, outcome data are still based on observational and post hoc analyses as most randomised HF trials excluded patients with high serum creatinine (SCr) levels. Unfortunately, it is this group that most likely benefit from prognostic medications, of which the dosage and clinical prescription are often dependent on the underlying renal function (RF) [13]. The present literature highlights 3 important viewpoints: the renal perspective, the cardiac perspective and, lastly, the issue of therapeutics. Table 1 summarises the relevant large studies with epidemiological data on congestive heart failure (CHF) and CRI.

(i) The Depth of the Problem

The cardiovascular system maintains a direct communication with other organ systems; however, the cardiorenal interaction appears to be the most substantial. This is supported by the position statement from the National Kidney Foundation Task Force on cardiovascular outcomes in CKD: 'patients with CKD be considered in the ''highest risk group'' for subsequent cardiovascular events and that treatment recommendations based on cardiovascular risk stratification should take into account the highest-risk status of these patients' [13, 14].

HF is the most common admitting diagnosis in the United States for patients aged >65 years [15]. CKD is a worldwide public health problem with a rising incidence and a prevalence associated with poor outcomes and high cost. The US health system requirements for

Table 1. Epidemiology of RI in HF

First author [Ref]	Population	Participants	Age years	Female %	Black race %	Duration	RI prev/inc	Definition of CKD	Study design	ACM	CVM	Renal failure on CV endpoints
Sarnak [5]	General	5.8 m	NA	NA	NA	NA		NA	NA	NA	NA	NA
Velavan [120]	Suspected HF admissions	10,701	68	39	NA	90 days	17 NA	SCr	PC	+	+	SCr >103 μmol/l independent predictor; 12-week mortality OR 1.2 (95% CI 1.2–1.3, p < 0.001)
Patel [121]	ADHF	15,560	76	50.1	17.7	Length of hospitalization	6.6–44 NA	MDRD	PC	+	+	Ischaemic HF prevalence with stages of RF: normal 8.5%, mild 26.8%, moderate 43.9%, severe 14.2%, and renal failure 6.6%, p < 0.0001; increased inpatient mortality with increasing severity of RI
Heywood [9, 15]	ADHF	118,465	72.4	52	20	Length of hospitalization	See figure 2	MDRD	PC	+	+	See table 2
Fonarow [11]	ADHF	48,612	73.1	51.6	17.7	90 days	19.6 20.4	SCr	PC	+	+	WRF (7%); in-hospital mortality OR 1.48 (95% CI 1.23–1.79, p < 0.001); 60–90-day (509 patients) mortality 18.2% and rehospitalization 44.7%
Damman [33]	ADHF and CHF	18,634	59–79	16-67	NA	30 days to 4.8 years	Variable NA	SCr, eGFR	M-A	+	+	Increased ACM with worsening grade AKI
Coca [122]	Variable HF presentations	78,855	NA	NA	NA	30 days	3.2–60 NA	SCr	M-A	+	+	Increasing risk of 30-day mortality with worsening grade AKI using percentage change and absolute change of SCr to define AKI
Smith [123]	ADHF and CHF	80,098	52–79	9–100	NA	NA	NA 63	SCr	M-A	+	+	ACM of any RI OR 1.56 (95% CI 1.53–1.60, p < 0.001); severe RI OR 2.31 (95% CI 2.18–2.44, p < 0.001); WRF and 1-year mortality OR 1.47 (95% CI 1.26–1.72, p < 0.001)
Smith [13]	ADHF	53,640	79	58	11	1 year	NA 68	SCr, MDRD	RC	+	+	An increase in creatinine by 0.5 mg/dl is associated with an increase in the 1-year death risk by 10% in blacks and by 15% in whites
Lewis [124]	AMI	11,040	70	39.2	8.4	NA	6.3–8.5 10.3	eGFR	RCT	+	+	Increased risk of HF or CVM HR 1.12 (95% CI 1.08 –1.16, p < 0.001)
Shlipak [125]	AMI	130,099	77	46	7.7	1 year	16–41 NA	SCr, C+G	RC	+	+	Prevalence of HF with SCr <132 μmol/l = 16%; 132–212 μmol/l = 31%; 221–345 μmol/l = 41%; p < 0.001; no statistical interaction between LVEF <40 and >40%, RI and 1-year mortality using SCr to define RF
Stevens [126]	Elderly CKD	27,017	NA	66.7	24.5	NA	NA 55	MDRD	KEEP registry	NA	NA	CHF 4.2 vs. 7.5 RR (p < 0.001) in patients with vs. without CKD
Bertoni [127]	DM	151,738	75	60	12	5 years	18.6 39.3	NA	RC: America/ Medicare program	+	+	Nephropathy: prev HR 3.51 (95% CI 3.34–3.68), inc HR 1.53 (95% CI 1.46–1.5); ESRD: prev HR 1.43 (95% CI 1.25–1.63), inc HR 1.53 (95% CI 1.46–1.59)
Nichols [128]	DM	17,076	63	48	NA	4.7 years	NA 50.1	ACR, need for RRT	RC: Kaiser Permanente Northwest	+	+	micro HR 0.78 (95% CI 0.65–0.93, p = 0.006); macro HR 1.25 (95% CI 1.08–1.46, p = 0.004); ESRD HR 1.54 (95% CI 1.04–2.3, p = 0.032)
Go [19]	General: low risk	1.12 m	52	55	7.4	2.8 years	2.1 NA	MDRD	PC: Kaiser Permanente renal registry	+	+	eGFR (in ml/min/1.73 m^2): >60 (1.0%); 45–59 (5.2%); 30–44 (12.6%); 15–29 (20.8%); <15 (18.5%)

This table only includes the major studies in CRS epidemiology. We included studies above 5,000 patients.

ACM = All-cause mortality; ACR = albumin:creatinine ratio; ADHF = acute decompensated heart failure; AKI = acute kidney injury; AMI = acute myocardial infarction; C+G = Cockroft and Gault; CHF = congestive heart failure; CKD = chronic kidney disease; CVM = cardiovascular mortality; DM = diabetes mellitus; ESRD = end-stage renal disease; HF = heart failure; prev/inc = prevalence/incidence as reported in the original study; LVEF = left ventricular ejection fraction; M-A = meta-analysis; macro = macroalbuminuria; MDRD = Modification of Diet in Renal Disease; micro = microalbuminuria; NA = not available; PC = prospective cohort study; RC = retrospective cohort study; RCT = randomised controlled trial; RF = renal function; RI = renal impairment; SCr = serum creatinine in μmol/l; WRF = worsening renal function.

dialysis and transplantation exceeded 320,000 people in 1998 and surpassed 650,000 people within a decade. Iatrogenic renal replacement therapies are associated with a high mortality; in 45- to 54-year-olds, the cardiovascular mortality rate is 65 times higher than in the general population, and a more dramatic 500 times among younger cohorts [16]. A higher prevalence is noted for the earlier stages [5]. Although most of the traditional risk factors are prevalent in patients with CKD, studies have shown that the Framingham risk equation is insufficient to capture the extent of CVD, an important contributor to CHF, in patients with CKD. While this may result from the influence of non-traditional risk factors, it also highlights a unique entity with the potential for devastating and unpredictable consequences [15]. In patients with diagnosed CHF, significant RI is also common. Underlying RI contributes to poorer in-hospital outcomes and a grim prognosis [15, 17]. Worsening renal function (WRF) in the absence of primary renal disease is also a major determinant of outcomes in HF [15, 18].

(ii) Prevalence of HF with Varying Stages of CKD

When looking outside the broad classification of CVD, the prevalence of CHF among the different stages of CRI is actually not well established. Broadly extrapolating CVD data from CKD databases highlights mortality rates 10–30 times higher in dialysis patients and 5-fold higher after stratification for age [15]. While data are lacking in patients with CKD stages 1–4 (kidney transplant recipients) and CKD stages 3–4 (diabetic and non-diabetic kidney diseases), data from the Dialysis Morbidity and Mortality Study (Wave 2), United States Renal Data System Annual Data Report 1997, suggest a CHF prevalence of 40%. Proteinuria and microalbuminuria which act as surrogates for early non-diabetic CKD and early diabetic CKD are also associated with adverse CHF outcomes [5, 19], but actual rates are also still less well defined.

(iii) Prevalence of CKD in Patients with HF

Existing data support 4 important perspectives. Firstly, a high prevalence of CRI in CHF. Secondly, worse CHF outcomes when baseline RF is abnormal. Thirdly, admitted patients with WRF carry a significantly poorer prognosis. Fourthly, CRI is underdetected among HF patients who are at a higher risk of progression to end-stage renal insufficiency (ESRI).

Baseline RF and HF Outcomes

The ADHERE database, which was set up in October 2001, recorded data from 175,000 admissions across 280 participating centres from August 2005. From this database, Heywood et al. [15] were able to determine the prevalence and severity of RI at the time of hospital admission in patients with acute decompensated HF (ADHF), and to relate the degree of RI to treatments and in-hospital outcomes. It has been noted that previous large outpatient CHF studies excluded patients with RI; furthermore, the diagnosis was made solely on the basis of an elevated SCr level. The National Kidney Foundation has advocated eGFR using the Modification of Diet in Renal Disease (MDRD) formula for all patients, and thus the degree and impact of RI in HF based on SCr are likely underestimated [15, 20]. Hence, for the first time we have an accurate estimate of the prevalence and impact of the cardiorenal syndrome (CRS) on clinical outcomes. Table 2 summarises the major findings from the ADHERE database. The findings suggest a significant burden of CRI, worse outcomes and

Table 2. Major findings from the ADHERE database (modified from [14])

Baseline demographics	*In-hospital clinical outcomes*
1 Only 10,660 (9%) of the study population were classified as stage 1 (normal RF), while 63.6% were classified as either moderate or severe (stage V renal failure).	1 In-hospital outcomes worsened with grade of RI, inclusive of mechanical ventilation, ICU admission, cardiopulmonary resuscitation and new-onset dialysis.
2 Although 59.3% of men and 67.6% of women had at least moderate renal dysfunction at admission, only 33.4% of men and 27.3% of women were reported as having renal insufficiency in the database. Only less than 10% of patients with moderate renal dysfunction (stage III) had a baseline SCr level >2.0 mg/dl.	2 Length of hospital stay correlated with grade of baseline RI, except for stage V, which correlated with moderate RI.
3 MDRD-based eGFR predicts frequency of common risk factors, e.g. hypertension, diabetes and clinical atherosclerosis as manifested by coronary artery disease or peripheral vascular disease.	3 In-hospital mortality increased with severity of baseline RI. GFR remained an independent predictor of mortality (OR with 10 ml/min/1.73 m^2 decrease in GFR was 1.23; 95% CI 1.21–1.25).
4 The mean systolic ejection fraction was similar (37.3–37.8%) for all stages of kidney function except for stage V, where it was 40.3% ($p < 0.0001$).	4 Worsening of RF during hospitalization was also associated with increasingly unfavourable outcomes.

The ADHERE database, which was set up in October 2001, recorded data from 175,000 admissions across 280 participating centres from August 2005.

underprescription of disease-modifying therapeutics. Several smaller studies using CRI diagnosed based on eGFR highlighted RF as the most powerful prognostic indicator, exceeding functional status and ejection fraction [13, 15, 17, 21–27].

WRF and Outcomes

The ADHERE database has provided resounding evidence that even small to moderate decreases in RF are associated with significant morbidity and mortality, supporting multiple smaller studies [13, 15, 20, 28, 29]. Among 1,002 patients, Gottlieb et al. [27] showed that the majority had some increase in SCr, while 30% had a 20% increase. While any increase in SCr level was significant, an increase of 0.3 mg/dl had a sensitivity of 81% and a specificity of 62% in predicting either death or a length of stay of 10 days or more [20]. Systematic meta-analyses and smaller series have shown that a 0.2-mg/dl increase predicted a worse outcome, and an increase of 25% was a very specific marker of poor prognosis [30]; at discharge, 12% of patients had a 25% decrease in eGFR [31], and WRF developed in 27%, usually within 3 days of admission [32]. The severity of WRF was also associated with greater mortality [18, 33–36]. In addition, it has been shown that in children, death is more likely than progression to ESRI [37, 38].

Surprisingly, WRF occurs even in the absence of clear precipitants such as hypotension, shock or a procedure that requires contrast or bypass surgery [29]. Krumholz et al. [39] looked at 1,681 discharges among patients aged ≥65 years who did not have clear precipitants for RI. WRF was associated with male gender, hypertension, basilar rales, pulse >100 bpm, systolic blood pressure >200 mm Hg and admission SCr >1.5 mg/dl. Based on the number of these factors, a patient's risk for developing WRF ranged between 16% (1 factor) and 53% (5 factors). After adjusting for confounding effects, WRF was associated with a significantly longer length of stay by 2.3 days, higher in-hospital cost by USD 1,758 and an increased risk of in-hospital mortality (OR 2.72; 95% CI 1.62–4.58) [39]. Predictive models based on the ADHERE database to provide clinicians with a validated, practical bedside tool for mortality risk stratification have been developed. While models like these predict risk, they do not allow us to tailor therapy towards the individual patients with exacting accuracy; thus, the patients with the highest risk may be denied therapy based on conjecture rather than sound physiology [40].

Table 3. Therapeutics in HF and chronic renal failure

Therapy	Number of studies including sub-studies	Number of participants	Number of trials with information on method of RF assessment					Age years	Race[a]	Sex[b]	CKD as exclusion criterion[c]	Contra-indication in CRF	AKI or ↑ K^+ as adverse event	Post hoc analysis
			SCr	BUN	MDRD	C-G	NA							
Beta-blockers	10	19,687	6	0	1	0	4	49–64	2 (5–23)	17–27	7 (SCr >245.5 to >300)	No	No	1 – SENIORS
ACE-I	7	14,810	5	0	1	0	1	59–75	1 (9.5–15)	18–57	7 (SCr >151 to >300)	Relative	Marginal	2 – SOLVD, ATLAS, CONSENSUS
ATRA	6	15,713	2	0	4	0	0	62–71	6 (1–7)	20–60	6 (SCr >177 to >220)	Relative	Marginal	2 – V-HEFT, CHARM
Aldosterone antagonist	2	7,895	1	0	1	0	0	65	2 (1–13)	27–30	2 (SCr >220)	Relative	Yes	1 – RALES
A-HEFT	1	1,050	NA					56	1 (100)	59	NA – prevalence RI 16–18	No	No	No
Inotropes[d]	2	1,530	2	1	0	0	0	67	1 (<6)	12–28	1 (SCr >450)	No	No	No
Device	10	10,306	4	2	0	0	4	63–67	2 (8–23)	8–27	1 (SCr >265)	No	No	1 – MADIT

The table is inclusive of those therapies that provide acute and chronic prognostic benefit. Other non-prognostic therapies including diuretics were not included. All data are expressed as number of studies or cumulative upper and lower values. AKI = Acute kidney injury; BUN = blood urea nitrogen in mmol/l; C-G = Cockcroft-Gault formula; CRF = chronic renal failure; K^+ = serum potassium; NA = not available. SCr was measured in μmol/l.

[a] Race: number of studies which included black race as participants, with cumulative lower and upper range as percentage of study population in parentheses. [b] Sex: cumulative lower and upper range of participants as percentage of study population who were female. [c] CKD: number of studies that excluded CKD patients and criterion provided, with cumulative method used to define CKD and lower and upper values used to define CKD in parentheses. [d] Levosimendan trials only.

Progression to ESRD and Underestimation of CRI

Among randomly selected Medicare beneficiaries with a diagnosis of CHF or acute myocardial infarction, the prevalence of CRI, based on the estimated MDRD GFR of <60 ml/min/1.73 m^2, was 60.4%. ESRI after discharge occurred in 32/640 patients (OR 34.5; 95% CI 4.23–429.43); only 1 patient had an eGFR >60 ml/min/1.73 m^2. Many of those who progressed to ESRI did not have a diagnosis of CRI at discharge. Even at the most severe degrees (MDRD-estimated GFR of <30 ml/min/1.73 m^2), fewer than half had a diagnosis of CRI. Among the 24 CHF patients who developed CRI, only 20% were discharged with that recorded diagnosis. These data suggest that there are substantial opportunities to improve the detection of CRI in those patients who are hospitalized with CHF [33, 41].

Therapeutics in HF and CKD

The only proven therapies for CHF are pharmacological treatments as the first line, device therapy as the second line and cardiac transplantation when the others fail. Unfortunately, when therapy is omitted, these patients are relegated to the placebo arm of HF trials, with ongoing exposure to the detrimental independent effects of impaired RF; in other words, a 'double whammy'. Most major randomised controlled CHF trials, except for CHARM, excluded patients with moderate to advanced CRI and infrequently performed subgroup analysis. Furthermore, these trials predominately used SCr to determine RI. The Cardiovascular Health Study highlighted the inability to identify CRI in the elderly as SCr is not an effective measure of RF [42], which may raise doubts on the conclusions drawn from subgroup analysis. Table 3 summarises the medications and outcomes from the major HF trials. There is a clear consensus that all patients who have systolic dysfunction should be on an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB) if ACE-I is contraindicated, on hydralazine and isosorbide mononitrate if the latter are contraindicated, or on beta-blockers. For symptomatic patients and patients with more

severe forms of CHF, addition of aldosterone blockade has additional prognostic benefit, as does device therapy in carefully selected individuals [38]. The fear of iatrogenic side effects (WRF, hyperkalaemia) has consequently led to lower prescription rates in this vulnerable group [43]. These factors are, however, determined by estimating the underlying eGFR accurately. For the purposes of this review, we have focused the discussion specifically on CRS types 2 and 4. Treating the aetiology is the common denominator in the management of all types of the CRS. Prognostic HF therapy is also indicated in all types; the severity and chronology of comorbid illness as well as the physicians' confidence may influence individual prescribing practices [7].

Interventions Targeted at Prevention and Risk Factor Control

There are numerous other factors that secondarily affect outcomes. While treatments of each of these factors have not been proven to affect outcomes, they nonetheless reflect the severity of the underlying disease state and thus warrant treatment and improvement of the primary condition. One such factor is anaemia, which may reflect both worsening GFR and anaemia of chronic illness related to the severity of HF. This in itself is independently associated with poor outcomes. The fact that measures to secondarily improve the haemoglobin level have not affected outcomes is further evidence that pharmacological measures aimed at improving cardiac function and preventing deterioration of GFR are paramount [44–48].

Diabetes and the intensity of glycaemic control remain an area of significant controversy. Type 2 diabetes mellitus and insulin resistance are associated with an increased HF risk and risk of progression. A 1% increase in haemoglobin A1c may increase the HF risk by 8%; this association follows a U-curve, with excess mortality with lower haemoglobin A1c (<6.4%) as well. The risk of HF hospitalizations is, however, linear [49–53]. Poor glycaemic control patients have poor in-hospital and long-term outcomes. These patients are more likely to present in advanced New York Heart Association class, CHF or RI [54, 55]. Several recent meta-analyses have added some confusion. The first, a meta-analysis of 7 studies with 34,144 participants, supported intensive glucose control with reduction on major cardiovascular events with no effects on all-cause mortality and HF at the expense of an increased hypoglycaemic risk [56]. A further meta-analysis of 13 studies including 34,533 patients showed limited benefit of intensive control on all-cause mortality and cardiovascular death, with a 2-fold increase in hypoglycaemia and a 47% increase in CHF risk [57]. With regard to therapy, metformin remains the only antiglycaemic agent with demonstrated prognostic benefit, but a HF-targeted prospective study is lacking. Thiazolidinediones are the only agents with proven adverse HF risk. The extent to which manipulation of glucose control effects the sympathetic or renin-angiotensin-aldosterone system (RAAS) activity in the CRS has not been explored. In temporal terms, glucose control is highly sensitive to therapy. The dependence of counterregulatory effectors in CRS haemodynamics would suggest caution and a gentle approach in regulating metabolic derangements [51, 58].

Tonelli et al. [59] reviewed 1,711 participants in the CARE study followed up for a median of 58.9 months and noted that pravastatin was safe and effective for secondary prevention of cardiovascular events in persons with mild CRI (as defined by eGFR ≤75 ml/min/h; Cockcroft-Gault formula) but was underused in this setting. Various agents have reproduced these findings in microalbuminuric stages, CKD stages 2–3 and renal transplants. Observational data extend this benefit in ESRD. The only randomised study using atorvastatin did not reproduce these observations. An unexplained excess of stroke in the treatment arm and an overall mortality approaching 50%, where more than half were non-cardiac, highlight a vulnerable group with yet to be identified confounders in play. In addition, statins also reduce the rates of progression of CKD and offer protection from acute renal failure (ARF)

during cardiac procedures. Despite the small (0.5–2%) risk of liver biochemical abnormalities and myalgia or myopathy, the benefits significantly outweigh the risks [60, 61].

At the time of writing, the SHARP study conclusively showed benefit of lipid lowering in ESRI with simvastatin and ezetemibe [129]. While providing critical answers, it also raises questions on the class of agents with benefits, the role of ezetemibe, the discrepancies noted with combination therapies from earlier studies, and benefits with varying cause and stages of CKD. These are but a few questions in this advancing area.

Benefits of aspirin in vascular disease among CRI patients are unequivocal, although with potential to increase major bleeds and paradoxical thrombosis. Among hypertensive CKD patients, aspirin therapy was associated with greater absolute reductions in major cardiovascular events and mortality than with normal RF [62]. The physiological effect of aspirin on renal blood flow in HF is still contentious; as a single agent, it appears safe. In the CRS, if concomitant agents have negative effects on RF is unclear, but they seem unlikely to have a negative impact. Further studies should similarly demonstrate these positive effects. The availability of alternative oral antithrombotics adds encouragement for the overall safety in cardiorenal therapeutics [63–65]. The need for holistic care and secondary factors among CRS patients warrants consideration as well.

HF Medications

RAAS Blockade

Blockade of RAAS via ACE-I, all-trans retinoic acid (ATRA) and aldosterone is mainstay and alters prognosis positively. Foley et al. [66] noted that changes in echocardiographic parameters at inception compared to 1 year of dialysis for ESRD were associated with development of CHF, while regression of left ventricular abnormalities was associated with an improved cardiac outcome. In the CRS, WRF and hyperkalaemia are significant safety concerns for many physicians. Among 4,350 ADHF admissions, patients with the lowest eGFR levels were least likely to be prescribed ACE-I/ARBs or both ACE-I/ARB and beta-blockers [33]. The underprescription with worsening CRI has a clear mortality gradient. A small caveat was that, while most medications were associated with improved outcomes, patients with an eGFR 60 ml/min/1.73 m^2 using ACE-I did not share the same benefit [43]. The authors speculated a possible interaction with aspirin in lowering renal perfusion, but also highlighted a degree of complexity with confounders. In the SOLVD study, patients assigned to enalapril had a 33% greater likelihood of decreased RF but were older or had diuretic therapy or diabetes.

Using a higher definition of WRF of $\geq$0.5 mg/dl, ARF was not significantly greater in patients on preadmission ACE-I/ARB or diuretic use, while the rate of renal recovery was not significantly different whether or not SCr increased. Many larger studies define ARF as an increase in SCr of only 0.3 mg/dl compared to admission level; this relatively small increase may be insufficiently specific within the range of expected laboratory variation [67]. Defining decreased RF as a rise in SCr of $\geq$0.5 mg/dl (44 μmol/l) from baseline, as mentioned above, undoubtedly detects deterioration in RF; it does not carefully implement a policy of selecting appropriate doses, timing of medications and detecting severity of renal injury in elderly patients in whom lower levels of SCr may be associated with RI. Rates of renal artery stenosis are more significant in this age group [68], which also requires consideration when prescribing medications for the elderly. Within a sicker cohort of 256 patients, in 89 patients on ACE-I circulatory-renal limitations of hypotension, progressive renal dysfunction or hyperkalaemia accounted for 60 cases (23%) and other adverse events, e.g. cough, accounted for 24 cases. Compared with patients on ACE-I, patients with circulatory-renal limitations were older, had a longer history of CHF, lower systolic blood pressure, lower sodium and higher SCr. Mortality was 57% in patients with circulatory-renal limitations and 22% in patients on

ACE-I during a median follow-up period of 8.5 months (p = 0.0001); these data are supported by several other studies [69–71].

In short, the use of medical therapy appears to relate to the CRI stage. ACE-I or ATRA at discharge decreased markedly with increasing RI, using either SCr or eGFR. Our present understanding suggests a need for understanding the limitations of these tests and the inability of measured eGFR to provide a sound estimate of RF in the acute setting and SCr to diagnose CRI [7]. An editorial comment by Bart [72] suggests: 'ACE-I continue to be the best tolerated and most effective agents for improving symptoms, decreasing hospitalizations and prolonging survival in patients with HF however their use ranges from 35–80%. While the reasons vary from truly intolerant patients, real or perceived contraindications, poor compliance and variability in physicians practice. As there are few absolute contraindications, of the 7,487 patients in SOLVD only 11 (0.15%) had azotemia and average increase in SCr was 0.02 mg/dl. Despite this 6–17.5% of HF patients remain untreated because of real or perceived contraindications. While WRF is highly dependent on volume status, degree of sodium depletion and concurrent medications (B-Blocker appears protective), a strategy of patient preparation, premedication, diuretic dose monitoring, and accurate assessment of baseline RF and early detection of renal injury would seem a new direction in the use of these medications before they are relegated to a lifetime of absolute contraindication.'

Presently, recommendations to withdraw ACE-I should only occur when the rise in SCr exceeds 30% above baseline level within the first 2 months of initiation; in addition, a rise in SCr which gradually improves is a normal haemodynamic response to improvements in left ventricular function [73, 74]. As for cardiovascular mortality, all-cause mortality and HF hospitalization, the risk reduction was significantly smaller in those without RI than in those with RI. Thus, the frequent practice of withholding ACE-I in patients with CRI is unwarranted [75–77]. New data from the HOPE study further suggest that hyperkalaemia (<6.5 mmol/l) does not increase the risk of cardiovascular events, whereas hypokalaemia (<3.5 mmol/l), which is mitigated by ACE-I, is harmful [77]. These issues reinforce the need for careful monitoring and improvements in the learning curve [78–82].

Aldosterone blockade has proven to be beneficial in symptomatic CHF or CHF after acute myocardial infarction and has been shown to delay progression of CKD. Anecdotal evidence supports improvement in left ventricular end diastolic parameters in early CKD and elderly patients with more severe RI. Direct evidence is lacking as patients with SCr >221 μmol/l were excluded from randomised trials. Safety concerns, particularly hyperkalaemia, still plague its use in severe RI. Among the major CHF trials, hyperkalaemia (potassium >6 mEq/l) was 2–5.9% treatment versus 1–3.9%. Risk factors included eGFR <45 ml/min/1.73 m^2, older age, use of NSAID, potassium-promoting drugs or supplements and fluid balance not controlled for. RAAS blockade, beta-blockers and digoxin all contribute to hyperkalaemia in 5–10% of cases by suppressing aldosterone, although in most cases it is mild (0.1–0.3 mEq/l). Careful monitoring of these agents, serum digoxin levels, avoiding potassium supplements and NSAID, low-potassium diets, addition of potassium-wasting diuretics and increased vigilance in the lower GFR ranges and when serum potassium is >5.5 mEq/l will make a difference. Physicians should also consider halving doses or stop administration when levels are above 6 mEq/l. Another important consideration is the potential for GFR to decline further in ADHF. However, as there are no data for patients with eGFR <30 ml/min/1.73 m^2, the use of aldosterone blockade in the lower GFR ranges should be made at an individual patient level until diagnostic advances are available [83–88]. In ADHF when eGFR levels may decline, clinical judgement should be used. No trial will provide evidence in this regard.

Direct renin inhibitors have also shown promise in HF therapeutics and may have some relevance. Firstly, much is still unknown about the source of sympathetic nervous system

activity (SNSA) in CRI. Whether the juxtaglomerular apparatus is the source or effector of renal sympathetic nerve activity remains unclear; thus, consideration of renin inhibition at its source may warrant exploration. Secondly, pathophysiological observation of aldosterone 'escape', non-ACE generation of angiotensin II and a compensatory rise in renin and downstream RAAS effectors that may overwhelm ACE-I-blocking effects. As to which of these agents is used primarily or in combination to block the rate-limiting step in RAAS requires further exploration [89–91].

Beta-Adrenoceptor Blockade

Beta-blockers are the mainstay therapy for CHF, but debate still continues as to the principal class of drug as first choice in the CRS. The principles of prescribing remain similar; however, several additional factors require consideration [92–101]. Many CRS patients have an autonomous and chronically elevated SNSA, which affects remodelling of beta-adrenergic receptors and contributes to disease progression and poor outcome [102]. Anecdotal evidence suggests first-generation and non-selective beta-blockers may actually decrease GFR and renal blood flow, the effects of unopposed α_1ARs, while blocking A_2ARs-induced vasodilatation causes reflex sympathetic nerve activity and raises SVR/RVR leading to this reduction [103]; among second- and third-generation agents, carvedilol remains the strongest contender as agent of first choice from several small studies [104–106]. Of interest is nebivolol, a novel third-generation agent with NO-potentiating properties. A post hoc analysis from the SENIORS study revealed encouraging results; however, larger prospective studies are required [107, 108]. In a recent meta-analysis, Badve et al. [109] showed that beta-blockers significantly improved all-cause mortality. While this result is encouraging within the spectrum of the CRS, consideration for renal physiology and more severe RI in a well-designed prospective study is needed [44, 109]. The role of beta blockade in the CRS is evolving as we further understand the pathophysiology and deleterious impact of SNSA. The availability of direct sinus node inhibitors to control the chronotropic effects of SNSA without significant effects on haemodynamics, mood, fatigue, sexual function and RF (>15 ml/min/1.73 m^2) offers considerable promise for future studies [45].

Revascularization

The optimal mode of revascularization in ischaemic cardiomyopathy is still evolving. Early revascularization with functional evidence of ischaemia and viability from observational data may be associated with improved survival. There are, however, no randomised trials to support this, and significant confounders still plague the findings [110, 111]. Interestingly, among diabetics with a median eGFR 70 ml/min/1.73 m^2, medical therapy and percutaneous revascularization were equally beneficial. Rates from major cardiovascular events were, however, significantly lower in the surgical stratum. HF as an adverse complication occurred with equal frequency, 20% in both groups [112]. In addition when trials like CRUSADE are further scrutinized, at discharge the invasive groups are more likely to receive standard therapy, secondary preventive measures and support to modify risk factors [113]. In entirety, an individual's risk of renal deterioration with surgery and the lack of evidence for percutaneous revascularization highlight the need for meticulous planning and optimizing medical care in these patients. The decision on revascularization, mode and urgency needs to be made on a case-by-case basis with a high-risk mind-set [114–117].

Agents for Symptoms

Sodium and fluid balances with diuretics are the mainstay for symptomatic HF and RF. They offer no prognostic benefit. The advantages of potassium depletion have to be balanced with the risk of further impairing RF and physiological adaptations such as diuretic resis-

tance, thiazide (GFR <40 ml/min/1.73 m^2) and loop (GFR <30 ml/min/1.73 m^2). Digoxin improves symptoms and reduces CHF hospitalizations. It is 85% renally excreted; as such, higher levels are maintained with GFR <50 ml/min/1.73 m^2 and levels >1.2 ng/ml are associated with worse outcomes. These factors have to be considered when digoxin is used simultaneously with other prognostic medications with care and consideration for dosing, drug levels and serum biochemistry monitoring, diet modifications and multidisciplinary involvement are essential [83, 92].

Prescribing Practices for CRS Patients

As highlighted, undertreating patients does not lead to improved outcomes where the baseline risk is dismal to start with. Poor judgment in the timing of introducing an agent, starting dose, interval in increasing the dose and combination with other agents can also contribute to poorer outcomes. Are there simple strategies we can observe? The American Society of Nephrology and other national bodies have published recommendations for pharmacological prescriptions in RI. These guidelines should form the basis for most practices. We are keen to highlight several additional pointers that may be considered in patients with varying forms of the CRS:

Prognostic Therapeutics. There is never a good time to withhold or start a therapeutic agent with prognostic benefit. Most of the studies (studies on inotropes excluded) enrolled class 1 or 2, and stable class 3 or 4 patients. The study population was not confounded by comorbidities and electrolyte instability as is common in RI. The eventual benefit of these agents comes from the long-term use and dosing regimen that alter systemic physiology. Several agents such as RAAS and aldosterone blockade may have early symptom benefit. We recommend that if an agent is considered for the former purpose, it be withheld until a degree of clinical stability is guaranteed.

Physiological Considerations. If a chronic patient is haemodynamically brittle, admission to optimize therapeutics is an option. We recommend starting with a short-acting RAAS blockade, e.g. captopril, or lowest-dose aldosterone blockade, e.g. spironolactone 12.5 mg daily or alternate day. Absolute contraindications are >30% deterioration of RF, change in functional status or urine output, blood pressure <80/50, heart rate <50 bpm or serum potassium >6.0 mmol/l. We have stated these parameters at the lower or upper end of convention as these are often the clinical scenarios faced by physicians. A contraindication in these situations should not stay a contraindication indefinitely. The intervals at which doses are increased should be individualized.

Clinical Goal Setting. This is an important consideration. It should be considered early in the patient's consultation. The complexity of the problem should be highlighted to patients, and they should be active partners in the decision-making and follow-up. In all cases, prognostic medications at the maximum tolerated doses should be the goal. When there is deviation from this, the reasons should be highlighted to the patient and physicians sharing the care with the client. If the goal is proscription or suboptimal therapy, reasonable intervals should be stipulated to reassess the goals. Far too often, CRS patients are provided a goal that may be suboptimal or could contribute to future complications, which remain indefinitely.

Choice of Agent. The underlying aetiology of the organ primarily impaired, comorbidities, e.g. diabetes, baseline haemodynamics, e.g. heart rate, blood pressure, and serum potassium can determine the first agent to be introduced. Whether it is better to introduce one agent at the highest tolerated dose or several at low doses is unclear. Targeting clinical goals such as heart rates of 60–70 bpm in CHF or measures to reduce intraglomerular pressures and proteinuria may help clinicians moving forward.

Cardiorenal Med 2012;2:281–297
DOI: 10.1159/000342487
Published online: October 31, 2012

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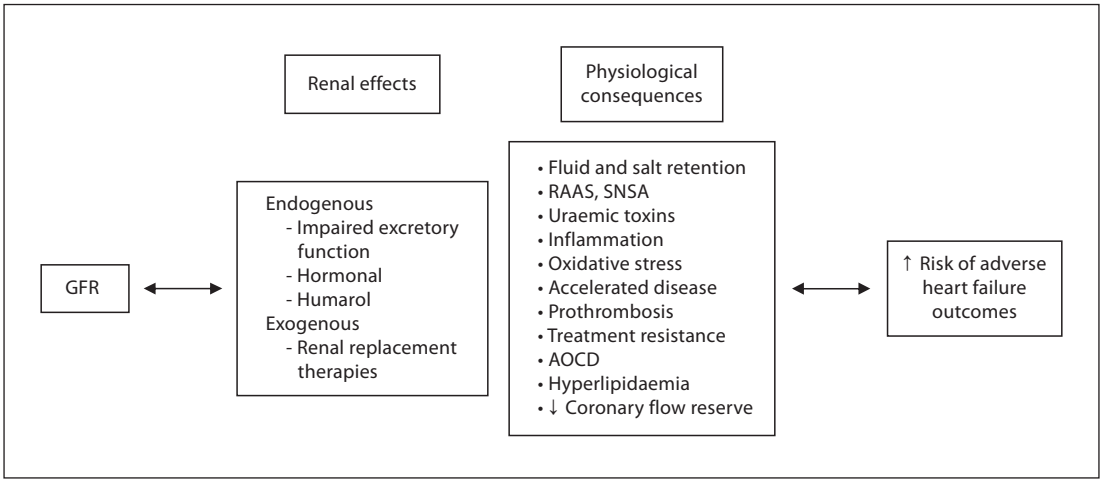

Fig. 1. Contributors of adverse outcomes in RI. As GFR progressively declines, there is a diminishing capacity to maintain excretory and endocrine function. Through the imbalance of the immune-neuro-hormonal axis, retained uraemic toxins and later renal replacement therapies, HF risk develops or is propagated at an accelerated rate.

Device Therapy

A subgroup analysis from the MADIT-2 study showed that the risk of sudden cardiac death increases with declining RF; however, the benefits of ICD therapy appears to be attenuated in patients with advanced renal disease [118, 119]. While this conclusion may hold true, the group with more advanced renal disease was statistically significantly older (>65%), more likely to be NYHA class >2, hypertensive, diabetic, had previous coronary artery vein bypass graft, QRS duration >0.12 s, lower ejection fraction (<25%), higher heart rates of <80 bpm and were less likely to be on ACEI, beta-blockers, lipid-lowering therapies and more likely to be on diuretics. Each of these characteristics alone point toward a higher-risk group with lower rates of pharmacological treatments [118], thus the need for prevention of sudden cardiac death requires equal baseline therapeutics in patients with eGFR in all ranges. It would appear that device therapy is not an alternative to conventional pharmacotherapy but complements optimal medical care. The inability to provide baseline pharmacotherapy should raise 'alarm bells' among physicians. Presently, an approach of considering these patients in the high category while providing closer observation and creative prescribing methods through a multidisciplinary approach may seem reasonable, at least until novel diagnostic and therapeutic therapies are clinically available. Figure 1 summarises the factors contributing to poor HF outcomes with RI.

Conclusion

Although we have known of the existence of the CRS, only recently have we understood the extent of the clinical significance backed by prospective evidence. This raises the issue of approach for these patients. Firstly, it is clear that we have underestimated the extent of the disease burden. Secondly, the tools we use are subject to multiple variables, and thus accuracy becomes a factor. Thirdly, clinical decisions are initially made on SCr and currently on eGFR; the consequences of the decisions have significant prognostic implications for the patients. While there are no actual guidelines or models we can use to predict with certainty

patients likely to develop WRF, the evidence supports significantly worse outcomes when treatments are denied. Clinical tools are required that can detect the onset of renal injury and failure earlier in the clinical course to support timely clinical decisions. The two issues raised above call for a unique approach to the CRS. This would entail improving the temporal profile of diagnosing AKI and increased accuracy in estimating baseline RI. We are currently awaiting the outcomes of several prospective diagnostic and therapeutic studies. These should tell us where to direct future research in the area. We would also encourage future studies to be more inclusive of patients with more advanced RI. Finally, it is important that treating physicians be aware of the increasing burden of such patients, the associated risks and the importance of pharmacotherapy in improving outcomes.

Disclosure Statement

All authors have individually received funding from the government and industry for studies in the CRS, but none pose a conflict of interest for this short review.

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