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Review Article

Heart-Kidney Interaction: Epidemiology of Cardiorenal Syndromes

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Cardiac and kidney diseases are common, increasingly encountered, and often coexist. Recently, the Acute Dialysis Quality Initiative (ADQI) Working Group convened a consensus conference to develop a classification scheme for the CRS and for five discrete subtypes. These CRS subtypes likely share pathophysiologic mechanisms, however, also have distinguishing clinical features, in terms of precipitating events, risk identification, natural history, and outcomes. Knowledge of the epidemiology of heart-kidney interaction stratified by the proposed CRS subtypes is increasingly important for understanding the overall burden of disease for each CRS subtype, along with associated morbidity, mortality, and health resource utilization. Likewise, an understanding of the epidemiology of CRS is necessary for characterizing whether there exists important knowledge gaps and to aid in the design of clinical studies. This paper will provide a summary of the epidemiology of the cardiorenal syndrome and its subtypes.

1. Introduction

On a global scale, evolving changes in demographics have lead to an aging population along with increasing rates of obesity, diabetes mellitus (DM), and hypertension. These emerging pandemics have also focused considerable attention on the public health importance and the broad implications of increasing rates of heart disease, kidney disease, and the concomitant occurrence of both heart and kidney disease.

An estimated 1 in 3 adults in the United States of America (USA) (or greater than 80 million persons) has a diagnosis of cardiovascular disease (CVD) (i.e., hypertension, coronary heart disease (CHD), heart failure (HF), stroke, or congenital heart disease) [1]. In the USA, the prevalence of any stage CKD has been recently estimated at 13% representing close to 30 million adults [2]. CKD has also emerged as an important and potentially modifiable predictor of CVD, including CHD, left ventricular hypertrophy, and HF [3]. Increasingly, there is recognition of the considerable clinical overlap and complex pathophysiology between CKD and CVD [4]. Cardiovascular disease may account for greater than 50% of all deaths in patients with CKD, occurring at rates 10- to 20-fold higher than an age-matched non-CKD population [5, 6]. This epidemic of CKD has potential far-reaching economic implications, as patients with CKD are more likely to be hospitalized, consume greater health resources, and have higher costs of care, both of which are increased further after progression to ESKD [7].

A description of the epidemiology of heart-kidney interactions is critical to understanding not only to overall burden of disease for each of the proposed CRS subtypes, but also their natural history, risk factors, associated morbidity and mortality, and potential health resource implications [8]. Likewise, an appreciation for the existing literature on the epidemiology and outcomes of CRS is necessary for recognizing whether there are important knowledge gaps and for the design of future observational studies and clinical trials. This paper will summarize the epidemiology and clinical outcomes associated with the CRS stratified by its subtypes.

2. Type 1 Cardiorenal Syndrome: Acute Cardiorenal Syndrome

The Acute Cardiorenal Syndrome (Type 1 CRS) is characterized by acute worsening of heart function leading to acute kidney injury (AKI) and/or dysfunction. Acute cardiac events that may contribute to AKI include acute decompensated heart failure (ADHF), acute coronary syndrome (ACS), cardiogenic shock, and cardiac surgery-associated low cardiac output syndrome.

Mostly commonly, observational studies have evaluated the development of AKI in association with ADHF and ACS (Tables 1 and 2). Many of these studies are limited in scope due to being performed retrospectively or being secondary and/or post hoc analyses from large databases [9–13] or secondary or analyses of clinical trials of drug therapy [8, 14, 15].

Most of these studies also use the term "worsening renal failure (WRF)" to describe the acute and/or subacute changes in kidney function that occurs following ADHF or ACS. For example, WRF has been defined as increases in serum creatinine (SCr) ≥26.5 μmol/L (0.3 mg/dL) [10, 13–16, 25–27], ≥44.2 μmol/L (0.5 mg/dL) [9, 10, 12, 13, 27, 28], ≥25% relative to SCr at the time of hospital admission, ≥50% at the time of hospital admission, and as the combined increase of ≥26.5 μmol/L (0.3 mg/dL) and ≥25% increase [17]. Stud-ies have also evaluated WRF as even smaller increments of rise in SCr (≥8.8 μmol/L (0.1 mg/dL)) [10, 12, 27] or as rate of decline in estimated GFR (eGFR) [29]. Aronson et al. evaluated WRF defined by a 50% increase in blood urea nitrogen above admission values [30]. Incidence estimates of WRF associated with ADHF and ACS have ranged between 24%–45% and 9%–19%, respectively. A small single center study found that AKI occurred in 48% of pediatric patients admitted for ADHF [31]. This wide range in incidence is attributed to differences in the definitions used for WRF, in the observed time-at-risk after hospitalization, and due to heterogeneity of the study populations.

Studies have used variable durations of observed time-at-risk for ascertainment of WRF. For example, in a cohort admitted with ADHF, Gottlieb et al. showed that 47% had WRF within three days of hospitalization [10]. Cowie et al. found that 50% occurred within four days [25]. Whereas, two observational studies found that 70%–90% of all WRF had occurred within the first week of hospitalization [11, 25]. Still, other studies have observed for WRF for 2 weeks [14] and up to 6 months [32]. These variations in ascertainment for WRF have the potential to introduce bias and misclassification. The most common definition for WRF has been any time within hospital admission [10, 11]. However, data have shown that the vast majority of WRF occurs early after hospital admission. Moreover, it is important to recognize that the pathophysiology of WRF/AKI likely varies at different time points. For example, WRF at presentation may be due to congestion and low cardiac output; however, investigations (i.e., cardiac catheterization and contrast media exposure) or interventions (i.e., furosemide, angiotensin converting enzyme [ACE] inhibitors) may impact kidney function and contribute, in part, to late WRF. These potential influences have not been well described in terms of time of onset of WRF.

The pathophysiologic mechanisms leading to WRF in ADHF are numerous and complex, but likely include alterations to cardiac output and systemic hemodynamics compromising kidney perfusion [33, 34] and pathologic compensatory neurohormonal activation [35]. An important risk factor also includes baseline kidney function and presence of CKD [19, 36]. Aronson et al. recently showed that persistent WRF after admission for ADHF was more likely in those with worse baseline kidney function [18]. Few studies have investigated the time course of WRF and whether there are observed differences in clinical outcome associated with transient WRF or persistent stepwise declines in kidney function after hospitalization for ADHF. Recently, Aronson et al. investigated this issue in a cohort of 467 patients admitted with ADHF [18]. WRF was defined as an absolute increase in SCr ≥ 44.2 μmol/L, whereas transient was defined as return to baseline within 30 days and persistent WRF as a sustained increase in SCr ≥ 44.2 μmol/L beyond 30 days. Of those developing WRF (33.9%), transient and persistent WRF occurred in 7.9% and 14.3%, respectively. At 6 months, mortality was 17.3%, 20.5%, and 46.1% in those with neither, transient and persistent WRF ($P < .0001$ for persistent versus no WRF), strongly suggesting a worse prognosis for those with persistent declines in kidney function.

Two studies have recently evaluated the association of novel biomarkers for predicting AKI/WRF in patients with AHDF [37, 38]. In a small cohort of 91 ADHF patients, serum neutrophil gelatinase-associated lipocalin (NGAL) was measured at the time of admission [37]. In total 35 patients (38%) developed WRF defined as an increase in SCr ≥ 26.5 μmol/L. In patients developing WRF, serum NGAL was significantly higher (194 ng/mL versus 128 ng/mL, $P = .004$). Those with an admission serum NGAL ≥ 140 ng/mL had a 7.4-fold increased risk of developing WRF. In another small cohort of 125 heart failure patients, Pfister et al. found elevated baseline NT-pro-BNP predicted subsequent AKI [38].

In both ADHF and ACS, AKI has consistently shown association with higher morbidity and mortality [11, 20, 45]. In ADHF, AKI is associated with increased risk for both short- and long-term all-cause and cardiovascular mortality [10, 11, 15–17, 19, 20, 25, 45]. In addition, data suggest that there is a biological gradient between AKI severity and mortality [27]. Several studies have shown development of AKI in association with ADHF prolonged stay in hospital [10, 11, 15–17, 19, 20, 25, 45]. Selected studies have also found that AKI in ADHF was associated with increased readmission rates [16, 17, 19, 45]. Recently, in a retrospective study of 20,063 Medicare beneficiaries hospitalized for ADHF, Kociol et al. found that 17.8% developed AKI (defined as an increase in SCr ≥ 27 μmol/L), with 64.5% readmitted and 35.4% dying within 1 year [20]. After adjustment for covariates, AKI was independently associated with long-term mortality (HR 1.12, 95% CI, 1.04–1.20).

AKI associated with ACS increases the risk of poor outcome [9, 12–14, 22–24, 28]. Even small acute changes

Table 1: Summary of studies fulfilling criteria for Acute Cardiorenal Syndrome (CRS Type 1) with a presenting diagnosis of acute decompensated heart failure.

Study	Population	Study type (data source)	AKI (WRF) definition	Incidence AKI (%)	Cardiac disease	Outcome
Nohria et al., 2008 [15]	$n = 433$ Mean Age 56 yrs Male % DM 34% HTN 47%	Retrospective (ESCAPE Trial)	SCr > 26.5 μmol/L	29.5	Hospitalized ADHF	All-cause death (6 m) (HR) increased for SCr > 106.1 AKI (>26.5 μmol/L) not associated with death/readmission
Logeart et al., 2008 [16]	$n = 416$ Age 71 yrs Male 59% DM 23% HTN 42%	Prospective	SCr > 26.5 μmol/L	37	Hospitalized ADHF Prevalence: LVEF 0.35 LVEF ≤ 0.45 70% Prior HF 45% Prior MI 55%	All-cause death (6 m) or Readmission (adj-HR) 1.74 Increased LOS 3 d Risk persisted whether AKI transient or not
Metra et al., 2008 [17]	$n = 318$ Mean Age 68 yrs Male 60% DM 34% HTN 53%	Prospective	SCr > 26.5 μmol/L & ≥ 25%	34	Hospitalized ADHF Prevalence: Prior MI 51% Prior HF 58%	CV death or readmission (adj-HR) 1.47 Increased LOS 7 d
Aronson and Burger [18]	$n = 467$	Prospective	SCr > 44.2 μmol/L	33.9 Transient 7.9 Persistent 14.3	Hospitalized ADHF	All-cause death (6 m) 17.3%, 20.5%, and 46.1% for no WRF, transient WRF, persistent WRF Adj-HR for persistent WRF 3.2 (95% CI, 2,1–5.0)
Belziti et al., 2010 [19]	$n = 200$	Retrospective	SCr > 26.5 μmol/L & ≥ 25%	23	Hospitalized ADHF	Higher mortality at 1-year ($P < .01$) Rehospitalization for WRF (HR 1.65, $P = .003$) Longer median LOS for WRF (9 versus 4 days, $P < .05$)
Kociol et al., 2010 [20]	$n = 20{,}063$	Retrospective	SCr > 26.5 μmol/L	17.8	Hospitalized ADHF	1-year mortality 35.4% (HR 1.12, 95% CI, 1.4–1.20) Rehospitalization 64.5%

SCr: serum creatinine; m: months; d: days; CV: cardiovascular; LOS: length of stay.

in serum creatinine modify the risk of death [14]. Among those developing AKIs, greater risk of cardiovascular events such as CHF, recurrent ACS, and stroke and need for rehospitalization have been shown [14, 23, 24]. Newsome et al. reported a greater likelihood of progression to ESKD in those with ACS complicated by AKI [12]. Recently, Goldberg et al. found increasing severity of and persistent AKI were associated with higher risk of death in patients surviving ST-elevation myocardial infarction (STEMI) [21]. This would imply, similar to studies with ADHF, that there is a biological gradient between AKI severity and duration and mortality.

These data would suggest that AKI in association with ADHF or ACS may further exacerbate cardiac injury and/or function and also contribute to exaggerated declines in kidney function. In a small cohort of 141 patients with reperfused anterior STEMI, those developing AKI were found to have higher plasma norepinephrine, BNP, interleukin-6 levels in the 2 weeks after reperfusion [23]. Moreover, those developing AKI have higher risk of in-hospital death ($P = .004$), major adverse cardiac events ($P = .02$), that correlated with greater observed left ventricular (LV) remodelling. This would imply that the observed heart-kidney interface in Type 1 CRS may synergistically act to further accelerate injury and/or dysfunction.

3. Type 2 Cardiorenal Syndrome: Chronic Cardiorenal Syndrome

This syndrome is characterized by chronic abnormalities in cardiac function leading to kidney injury or dysfunction. The term "chronic cardiac abnormalities" encompasses a number of different conditions and may include chronic LV dysfunction, atrial fibrillation, congenital heart disease, constrictive pericarditis, and chronic ischemic heart disease (Table 3).

Observational data clearly show that chronic heart and kidney disease commonly coexist, but such studies are unable to determine which of the two disease processes was primary versus secondary [46]. This therefore presents challenges when appraising the literature and attempting to classify patients into the CRS subtype definitions; it has been

Table 2: Summary of studies fulfilling criteria for Acute Cardiorenal Syndrome (CRS Type 1) with a presenting diagnosis of acute coronary syndrome.

Study	Population (n)	Study type (data source)	AKI (WRF) definition	Incidence AKI (%)	Cardiac disease	Outcome
Newsome et al., 2008 [12]	n = 87,094 Mean Age 77 yrs Male 50% DM 28%–37%	Retrospective (CCP)	Variable	Any 43.2 △SCr Quartiles: Q1: △0.1, 13.1; Q2:△0.2, 9.3; Q3: △0.3–0.5, 12.3; Q4: △0.6–3.0, 8.4	AMI Prevalence: Prior MI 31%–35% Prior HF 21%–35%	All-cause (death (1000 p-y)/HR): Q1 146/1.1; Q2 157/1.2; Q3 194/1.3; Q4 275/1.4 ESKD (incidence (1000 p-y)/HR): Q1 2.3/1.5; Q2 3.6/2.0; Q3 6.3/2.4; Q4 20/3.3
Parikh et al., 2008 [13]	n = 147,007 Age 76–78 yrs Male 49%-50% DM 29%–41%	Retrospective (CCP)	△SCr (μmol/L): Mild (26.5–35.4); Mod (44.2–88.4); Severe (≥88.4)	Any 19.4, Mild 7.1, Mod 7.1, Severe 5.2	AMI Prevalence: Prior AMI 30%–36% Prior HF 19%–35%	All-cause (10 yr) (death (crude%)/adj-HR): None 68/1.00; Mild 79/1.15; Mod 88/1.23 Severe >90/1.33
Goldberg et al., 2009 [21]	n = 1957 Age 59–70 yrs Male 79.4% DM 26.2%	Retrospective	△SCr (μmol/L): Mild (26.5–44.2), Mod-Severe (>44.2)	Mild 8.0 Mod-Severe 7.1	Prior AMI 20.9%	Adj-HR mortality: Mild transient 1.2; Mild persistent 1.8; Mod-severe transient 1.7; Mod-severe persistent 2.4
Mielniczuk et al., 2009 [22]	n = 3795	Retrospective	SCr > 25% over 1-month	5	—	Adj-HR 1.6 (95% CI, 1.1–2.3) for composite CV death, recurrent ACS, HF or stroke
Anzai et al., 2010 [23]	n = 141 Age 63 yrs Male 87% DM 36%	Prospective	SCr > 26.5 μmol/L within 48 hrs	22	Anterior STEMI	Higher in-hospital death (P = .004) and major adverse cardiac events (P = .02)
Marenzi et al., 2010 [24]	n = 97 Age 63–69 yrs Male 69% DM 18.6%	Prospective	SCr > 25%	55	STEMI + IABP	In-hospital death (RR 12.3, 95% CI, 1.8–84.9, P < .001). AKI associated with age > 75 yrs, LVEF < 40%, mechanical ventilation.

WRF: worsening renal function; SCr: serum creatinine; wks: weeks; m: months; CKD: chronic kidney disease; ESKD: end-stage kidney disease.

suggested to use the term Type 2/4 in these situations [8]. Large database studies often describe patient populations based on the existence of one disease process (i.e., HF) and subsequently estimate the occurrence of the other (CKD).

In the ADHERE study, a large dataset of 118,465 individual hospitalizations for ADHF, 27.4%, 43.5%, and 13.1% of patients were found to have mild, moderate, and severe kidney dysfunction at hospital admission [39]. Greater severity of kidney dysfunction correlated with worse clinical outcomes, including need for ICU admission, need for mechanical ventilation, longer hospitalization, and higher mortality. In the Digitalis Investigation Group trial, preexisting CKD was found in 45% of chronic HF patients and was associated with higher rate of hospitalization and death [39]. There was also evidence of a biologic gradient between CKD severity and outcome.

The Atherosclerosis Risk in Communities (ARIC) and Cardiovascular Health (CHS) studies recently provided some additional insight on the epidemiology of Type 2 CRS [40]. Patients with baseline CVD comprised 12.9% of the study cohort. At study entry, these patients had a mean SCr 79.6 μmol/L and estimated GFR 86.2 ml/min/1.73 m^2. After an average follow-up of 9.3 years, 7.2% of CVD patients had declines in kidney function when defined as an increase in SCr ≥ 35.4 μmol/L and 34% when defined as a decline in eGFR ≥ 15 ml/min/1.73 m^2. During follow-up, 5.6% developed new CKD. By multivariable analysis, baseline CVD was independently associated with both decline in kidney function and development of new CKD. These data strongly suggest that CVD is an important risk for measurable declines in kidney function (OR 1.70, 95% CI 1.36–2.31) and CKD (OR 1.75, 95% CI 1.32–2.32) and empirical proof of the concept of Type 2 CRS.

One clear example of CRS Type 2 is congenital heart disease, in which the heart disease temporally precedes any kidney disease. "Cyanotic nephropathy" (CN) has long been

Table 3: Summary of studies fulfilling criteria for Chronic Cardiorenal Syndrome (CRS Type 2).

Study	Population (n)	Study type (data source)	Cardiac disease	CKD	Cardiac-specific outcomes	Outcomes (%)
Heywood et al., 2007 [39]	N = 118,465 Mean Age 61.7–76.3 yrs Male 42%–57%	ADHERE registry	ADHF	eGFR 60–89: 27.4%; eGFR 30–59: 43.5%; eGFR 15–29: 13.1%; eGFR < 15: 7%	Use of cardioprotective meds (ACE-I and ARB) decreased with increasing degree of CKD	OR for in-hospital mortality: eGFR ≥ 90: 1.0; eGFR 60–89: 2.3; eGFR 30–59: 3.9; eGFR 15–29: 7.6; eGFR < 15: 6.5
Elsayed et al., 2007 [40]	N = 13826 Mean Age 58 yrs Male 56%	Prospective (ARIC and CHS)	Baseline CVD in 12.9%	eGFR decrease of at least 15 ml/min/1.73 m^2 to a final level < 60 ml/min/1.73 m^2 was seen in 34% of patients with baseline CVD	NA	OR for development of kidney disease 1.54 (CVD versus non-CVD)
Ahmed et al., 2007 [41]	N total = 7788 Mean Age 59.9–65.4 yrs Male 76%–81%	Retrospective (DIG trial); Propensity-matched study	Ambulatory patients with CHF	eGFR < 60 in 45%	A graded association was found between CKD-related deaths and LVEF	Matched HR: (CKD versus non-CKD) All-cause death 1.71
Campbell et al., 2009 [42]	N total = 7788 Mean Age 59.9–65.4 yrs Male 76%–81%	Retrospective (DIG trial); Propensity-matched study	Ambulatory patients with CHF	eGFR < 60 in 45%	Matched HR: (CKD versus non-CKD) CV hospitalization 1.17 HF hospitalization 1.08 CV death 1.24 HF death 1.42	Matched HR: (CKD versus non-CKD) All-cause hospitalization 1.18
Dimopoulos et al., 2008 [43]	N = 1102 Mean Age 36 yrs Male 48.5%	Retrospective (single center)	Adult congenital heart disease	eGFR 60%–89 41% eGFR < 60 9%	NA	All-cause death (HR) eGFR ≥ 90 1.0; eGFR < 60 3.25
Hillege et al., 2003 [44]	N = 298 Mean Age 51–67 yrs Male 70% DM 16%–27% HTN 6%–14%	Retrospective (CATS trial)	1st anterior wall MI	Change in GFRc Placebo: −5.5 ml/min/yr Captopril: −0.5 ml/min/yr	New CHF (RR) GFRc > 103: 1.0 GFRc 81–103: 1.23 GFRc < 81: 1.55	All-Cause death: 1-yr 8%

ARIC: atherosclerosis risk in communities study; ADHF: acute decompensated heart failure: GFRc: GFR estimated by Cockroft Gault; CATS: captopril and thrombolysis study; CVD: cardiovascular disease; CVS: cardiovascular health study; DIG: digoxin investigator group.

recognized as a potential complication of cyanotic congenital heart disease [47, 48]. Infants born with congenital heart defect, in the majority of circumstances, have normal kidneys. Dimopoulos et al. studied 1102 patients (mean age 36 yrs) surviving into adulthood with congenital heart disease [43]. Amongst this cohort, >50% had evidence of kidney dysfunction that was considered mild (eGFR 60 to 89 ml/min per 1.73 m^2) in 41% and moderate-severe (eGFR < 60 ml/min per 1.73 m^2) in 9%. Patients with Eisenmenger physiology had the lowest eGFR and the highest prevalence of moderate or severe reduced GFR (18%). Similarly, there was a trend towards greater kidney dysfunction in patients with more complex anatomy. However, kidney dysfunction was detected even among patients characterized as having "simple" defects. Importantly, kidney dysfunction had a substantial impact on mortality (propensity score-weighted HR 3.25, P = .002 for impaired versus normal GFR).

4. Acute Reno-Cardiac Syndrome (Type 3 CRS)

The Acute Reno-Cardiac Syndrome (Type 3 CRS) is characterized by acute worsening of kidney function that leads to acute cardiac injury and/or dysfunction, such as acute myocardial infarction, congestive heart failure, or arrhythmia. Conditions that may contribute to this syndrome include cardiac surgery-associated AKI, AKI after major noncardiac surgery, contrast-induced AKI (CI-AKI), other drug-induced nephropathies, and rhabdomyolysis.

The association of AKI and acute cardiac dysfunction with these conditions likely shares similar predisposing pathophysiologic mechanisms and risk factors for development (i.e., volume overload, systemic hypertension, retention of uremic solutes, hyperkalemia). However, the pathophysiologic mechanisms contributing to Type 3 CRS are likely to extend beyond simply retention of uremic solutes and/or volume overload. Defining the epidemiology of Type 3 CRS is challenging for several reasons. First, there is considerable heterogeneity in predisposing conditions causing AKI. Second, AKI has been variably defined across studies. Third, there is likely variable baseline risk for acute cardiac dysfunction across populations, such as increased susceptibility in selected individuals with subclinical cardiovascular disease. Finally, few clinical studies focused on AKI have reported on the event rates of acute cardiac dysfunction. Therefore, estimates of incidence and associated outcomes of acute cardiac dysfunction associated with AKI are largely context- and disease-specific.

For example, contrast media administration is a leading cause of iatrogenic AKI following diagnostic and interventional procedures and is associated with major adverse effects, progression of CKD, and consumption of health resources [49]. While AKI is most often attributable to the administration of contrast media, additional confounding factors, such as atheroembolic disease, renal hypoperfusion, concomitant nephrotoxins, may also be contributory. The reported incidence is highly variable depending on the population-at-risk being evaluated (i.e., age, CKD, DM, HF) and the type of procedure performed (i.e., emergent, intravascular, type, and volume of contrast media). Incidence estimates have been reported in the range of 1%–40% [49–51]. The natural history of CI-AKI in many patients may follow an asymptomatic rise in serum creatinine with early return to baseline, and these patients would not be expected to fulfill the criteria for Acute Reno-Cardiac Syndrome (Type 3 CRS). However, in an estimated 0.2%–1.1%, AKI progresses to require the initiation of renal replacement therapy (RRT) [49, 50, 52]. In these patients, AKI may be associated with volume overload, retention of uremic solutes, pulmonary edema, and cardiac arrhythmias. Importantly, those at-risk for developing CI-AKI requiring RRT may be identifiable *a priori*. However, the difficulty in evaluating the epidemiology of Acute Reno-Cardiac Syndrome (Type 3 CRS) attributable to CI-AKI is that few studies have specifically reported the temporal occurrence of cardiovascular events following contrast media exposure [53].

5. Chronic Reno-Cardiac Syndrome (Type 4 CRS)

The Chronic Reno-Cardiac Syndrome (Type 4 CRS) is a condition where primary CKD contributes a reduction in cardiac function, such as cardiac remodelling, left ventricular diastolic dysfunction or hypertrophy, and/or an increased risk for cardiovascular events, such as myocardial infarction, heart failure, or stroke. This CRS subtype refers to cardiac dysfunction and/or disease primarily occurring in response to CKD (Table 4).

Observational data have evaluated the cardiovascular event rates and outcomes in selected CKD-specific populations [54, 56, 57, 59–63]. Most have been retrospective and/or secondary post hoc analyses from large clinical registries or randomized trials. As mentioned above, this type of data cannot establish whether the primary process is the kidney disease (CRS Type 4) or the heart disease (CRS Type 2). Furthermore, defining the epidemiology of Type 4 CRS is challenging, and estimates are variable due to differences in (1) the populations-at-risk, (2) the clinical outcomes evaluated, (3) duration of time for ascertainment of study endpoints, and (4) the operational definitions used for defining CKD, cardiac disease, and/or mortality (i.e., all-cause or CVD-specific).

For example, the populations-at-risk in these studies, based on the presence and severity of CKD, ranged from near normal kidney function to ESKD. In a secondary analysis of the Hemodialysis (HEMO) Study, Cheung et al. found that 80% of ESKD patients had cardiac disease at enrollment [60]. Older patients, diabetics, and those having received a longer duration of maintenance hemodialysis (>3.7 years) had higher prevalence of pre-existing cardiac disease. During follow-up, 39.8% were admitted to hospital for cardiac-related diagnoses. Of these, 42.7% were attributable to ischemic CHD. Of the 39.4% of cardiac deaths, 61.5% were attributable to ischemic CHD. Baseline cardiac disease was significantly predictive of cardiac-specific death during follow-up (Relative Risk 2.57). Moreover, recent data have suggested that chronic maintenance hemodialysis induces repetitive myocardial injury and can accelerate declines in myocardial performance [64].

In CKD patients not receiving maintenance RRT, the prevalence of CVD varies considerably with CKD severity and the overall time-at-risk (i.e., duration of time with diagnosis of CKD) [58, 59, 62]. The risk of CVD events and death is also likely further modified by older age, comorbid illness, and presence of concomitant HF [54, 59, 62, 65]. In data from the NHANES II study, Muntner et al. found CVD prevalence of 4.5%, 7.9%, and 12.9% for patients with eGFR $\geq$ 90, 70–89, and < 70 mL/min/cm^2, respectively [55]. Likewise, in a large population-based cohort, Go et al. found similar graded increases in CVD prevalence and HF, along with higher risk of subsequent cardiac events during follow-up associated with degree of decline in eGFR < 60 mL/min/1.73 cm^2 [56]. This dose-response gradient in CVD prevalence by severity of CKD was also associated with higher trends in cardiac-specific and all-cause mortality [55–58]. Observational data have also shown that CKD accelerates the risk for and development of CVD [3, 59, 62]. This accelerated risk for cardiovascular events and disease in CKD may be the consequence of the unique pathophysiology that exists in these patients including hyper-homocysteinemia, elevated lipoprotein (a), oxidative stress, endothelial dysfunction, chronic inflammation (i.e., elevated C-reactive protein, interleukin-6), vascular remodelling (i.e., increased myocardial arteriolar wall thickness, reduced myocardial

Table 4: Summary of selected studies fulfilling criteria for Chronic Reno-Cardiac Syndrome (Type 4).

Study	Population (n)	Study type (data source)	CKD stage	Cardiac outcomes (%)	Outcomes (%)
Herzog et al., 1998 [54]	n = 34,189 Age ≥ 65 yrs 55% Male 56%	Retrospective (USRDS)	ESKD	Cardiac-Death: 1-yr 41%; 2-yr 52%; 5-yr 70.2%; 10-yr 83%	All-cause: 1-yr 59%; 2-yr 73%; 5-yr 90%; 10-yr 97%
Muntner et al., 2002 [55]	n = 6,534 Age 48–63 yrs Male 51%–61%	Retrospective (NHANES II)	eGFR < 70 75.9%	CV-Death (rate per 1000 p-y): eGFR ≥ 90: 4.1; eGFR 70–89: 8.6; eGFR < 70: 20.5	All-cause death (HR): eGFR ≥ 90: 1.00 eGFR 70–89: 1.64; eGFR < 70: 2.00
Go et al., 2004 [56]	n = 1.1 million Mean Age 52 yrs Male 45%	Retrospective (Kaiser Permanente)	≥ CKD stage III or eGFR < 60	CV Event (rate per 100 p-y/HR): eGFR 45–59: 3.65/1.4; eGFR 30–44: 11.3/2.0; eGFR 15–29: 21.8/2.8; eGFR < 15: 36.6/3.4	All-cause mortality (per 100 p-y/HR): eGFR 45–59: 1.1/1.2; eGFR 30–44: 4.8/1.8; eGFR 15–29: 11.4/3.2; eGFR < 15: 14.1/5.9
Foley et al., 2005 [3]	n = 1,091,201 Age ≥ 75 yrs 56.1 Male 39%	Retrospective (Medicare/USRDS)	CKD 3.8% (diagnostic coding)	CV Event Incidence: AMI 4–7 per 100 p-y; CHF 31–52 per 100 p-y; (HR 1.28–1.79)	All-cause death: HR 1.38–1.56
HIllege et al., 2006 [57]	n = 2,680 Mean Age 65 yrs Male 67%	Retrospective (CHARM)	eGFR < 60 36%	CV Death/Hosp. (HR) eGFR ≥ 90: 1.0; eGFR 75–89: 1.17; eGFR 60–74: 1.24; eGFR 45–59: 1.54 eGFR < 45: 1.86	All-cause death (HR) eGFR ≥ 90: 1.0; eGFR 75–89: 1.13; eGFR 60–74: 1.14; eGFR 45–59: 1.50 eGFR < 45: 1.91
McCullough et al., 2007 [58]	n = 37,153 Mean Age 53 yrs Male 31%	Retrospective (KEEP)	eGFR< 60 14.8%	Prevalence CVD (OR): eGFR ≥ 90 1.0; eGFR 60–89 1.1; eGFR 30–59 1.4; eGFR < 30 1.3	All-cause death (HR): CKD only 1.98; CVD only 3.02 CKD + CVD 3.80
McCullough et al., 2008 [59]	n = 31,417 Mean Age 45 yrs Male 24.5%	Retrospective (KEEP)	eGFR< 60 or ACR ≥ 30: 20.6%	Risk CVD/death (OR): CKD 1.44 No CKD 1.0	Worst survival for combined CKD and CVD at time of screening

ESKD: end-stage kidney disease; CKD: chronic kidney disease; DM: diabetes mellitus; HTN: hypertension; CHF: congestive heart failure; CVD: cerebrovascular disease; MA: microalbuminuria: CHD: coronary heart disease; LVH: left ventricular hypertrophy; CV: cardiovascular; eGFR: estimated glomerular filtration rate; ADHF: acute decompensated heart failure.

capillary density, increased cardiac interstitium [66]), alterations in platelet aggregation, neurohormonal activation, volume overload, reduced parenchymal mass, and deficiency in various hormones (i.e., vitamin D, erythropoietin) [67]. Another important consideration is that patients with CKD have often been excluded from clinical trials of interventions in CVD [4] and may receive less or suboptimal risk modifying and/or cardioprotective therapies, and perhaps as a consequence, receive less or suboptimal risk modifying and cardioprotective therapies such as aspirin, beta-blockers, and angiotensin-converting inhibitors despite evidence to suggest that CKD patients may similarly benefit [46, 68–70]. Finally, the genuine concern for treatment toxicities, intolerance, and/or risks in CKD patients or AKI may be such that therapy is not offered due to an unfounded perception of a less favourable risk-benefit ratio. These factors, in part, may provide explanation for the excess of CVD and associated poor outcomes for CKD patients.

Analogous to congenital heart disease being a prototype condition for CRS Type 2, genetic renal diseases can also be a similar example for CRS Type 4, in that the renal disease temporally precedes the cardiac disease. Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common genetic renal diseases worldwide and is the fourth leading cause of ESRD in the United States of America [71]. Cardiovascular complications are the leading cause of death in ADPKD, and multiple cardiac conditions have been described in these patients. As with CKD in general, the prevalence of left ventricular hypertrophy (LVH) is higher in ADPKD compared to a control population, and the frequency increases progressively as GFR decreases. However, several studies have also shown increased LV mass indices, LV diastolic dysfunction, and endothelial dysfunction in young otherwise normotensive ADPKD subjects with well-preserved renal function [72].

6. Secondary Cardiorenal Syndromes (Type 5 CRS)

The Type 5 CRS is characterized by an acute or chronic systemic illness that concurrently induces cardiac and kidney

Table 5: Summary of potential etiologies for acute and chronic Secondary Cardiorenal Syndromes (Type 5).

(a) Acute Systemic Illness
Severe sepsis/septic shock
Specific infections
HIV
Malaria
Leptospirosis
Hepatitis C virus
Drug toxicity
Cocaine
Heroine
Calcium-channel blockers
Cancer chemotherapy
Connective tissue diseases
Systemic lupus erythematosus
Scleroderma
Antiphospholipid antibody syndrome
Microangiopathy
TTP/HUS
Pregnancy
Malignant hypertension
Hemorrhagic shock
Vasculitis
Malignancy (i.e., lymphoma/leukemia)
(b) Chronic Systemic Illness
Hypertension
Diabetes Mellitus
Primary/Secondary Amyloidosis
Multiple Myeloma/Paraproteinemias
Sarcoidosis
Liver Cirrhosis
Primary/Secondary Pulmonary Hypertension

injury and/or dysfunction. Limited data is available on the epidemiology of Secondary Cardiorenal Syndromes due largely to vast number of contributing acute and/or chronic systemic conditions that may predispose to it. Accordingly, estimates of incidence, risk identification, and outcomes for Type 5 CRS are considered largely disease, and/or context-specific and may be time-varying. Importantly, there is currently an incomplete understanding of the pathophysiologic mechanisms of secondary cardiac-kidney interaction. Specifically, whether concomitant cardiac and kidney dysfunction in systemic illness is merely coexisting or whether there is genuine bidirectional interaction that may directly contribute to aggravated dysfunction in either organ system remains unclear (see Table 5).

Sepsis represents a prototypical condition that may cause an acute form of Type 5 CRS. Approximately 11%–64% of septic patients develop AKI [73], and 46%–58% have sepsis as a major contributing factor to development of AKI [74]. Observational data have shown higher morbidity and mortality for those with septic AKI when compared to either sepsis or AKI alone [74, 75]. Similarly, abnormalities in cardiac function are common in septic patients [76]. The incidence of cardiac dysfunction in sepsis is conditional on the population-at-risk being studied, the definition used for detection of cardiac dysfunction (i.e., troponin, B-type natriuretic peptide, pulmonary artery catheter, echocardiography), severity of illness, resuscitation, and duration of illness prior to evaluation. However, observational data have found that approximately 30%–80% have elevated cardiac-specific troponins that often correlate with reduced cardiac function [77]. Accordingly, coexisting acute kidney and myocardial dysfunction is common in sepsis; however, there is a lack of integrative and epidemiologic studies that have specifically evaluated the pathophysiology, incidence, risk identification, and associated outcomes for septic patients with concomitant AKI and myocardial depression who fulfill criteria for Type 5 CRS.

7. Conclusions

Considerable data from observational studies and clinical trials have accumulated to show that acute or chronic cardiac disease can directly contribute to acute or chronic worsening kidney function and vice versa. The Cardiorenal Syndrome subtypes are characterized by important heart-kidney interactions that share some similarities in pathophysiology, however, appear to have important discriminating features, in terms of predisposing or precipitating events, risk identification, natural history, and outcomes. The Type 1 CRS is common, with incidence estimates of AKI in ADHF or ACS between 24%–45% and 9%–19%, respectively. Type 1 CRS clearly translates into higher morbidity and worse clinical outcome. Chronic heart disease and CKD are increasingly prevalent and frequently coexist. Accordingly, this presents challenges for applying the proposed definitions for Type 2 and 4 CRS "retrospectively" to the existing literature when the primary versus secondary process cannot be clearly distinguished. The rate of progression of preexisting CKD in patients with established cardiovascular disease deserves further study, as well as the effect of cardioprotective therapies on these renal endpoints. Prospective research incorporating novel biomarkers of kidney-heart interaction is needed for better understanding of both Types 2 and 4 CRS, along with studies of CKD-specific interventions in Type 4 CRS. Due to heterogeneity, the incidence and outcome estimates associated Type 3 CRS are largely context- and disease-specific. Limited data is available on the pathophysiology or epidemiology of secondary Type 5 CRS. Accordingly, the epidemiology of Type 5 CRS is also largely disease- and context-specific. In summary, there is a clear need for additional prospective studies to characterize the epidemiology of heart-kidney interactions across the CRS subtypes, not only for a better understanding of the overall burden of disease, but also for risk identification and design of potential targets for intervention.

Disclosures

None to declare.

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