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]. Studies 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 hospital 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    | 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    | 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    | 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 Persistent 7.9 | 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) 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) 1-year mortality 35.4% (HR 1.12, 95% CI, 1.4–1.20) Rehospitalization 64.5% |
| Belziti et al., 2010 [19]    | n = 200    | Retrospective            | SCr > 26.5 μmol/L & ≥ 25% | 23                | Hospitalized ADHF | |
| Kociol et al., 2010 [20]     | n = 20,063 | Retrospective            | SCr > 26.5 μmol/L    | 17.8              | Hospitalized ADHF | |

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 $\triangle$SCR Quartiles: Q1: $\leq$0.1, 13.1; Q2: $\leq$0.2, 9.3; Q3: $\leq$0.3–0.5, 12.3; Q4: $\leq$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) | $\triangle$SCR ($\mu$mol/L): Mild (26.3–35.4); Mod (44.2–88.4); Severe ($\geq$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 $\geq$90/1.33 |
| Goldberg et al., 2009 [21] | n = 1957 Age 59–70 yrs Male 79.4% DM 26.2% | Retrospective | Mild 8.0 Mod-Severe 7.1 | Prior AMI 20.9% | | |
| Mielniczuk et al., 2009 [22] | n = 3795 | Retrospective | SCR > 25% over 1-month | 5 | — | |
| Anzai et al., 2010 [23] | n = 141 Age 63 yrs Male 87% DM 36% | Prospective | SCR > 26.5 $\mu$mol/L within 48 hrs | 22 | 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 | |

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 $\mu$mol/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 $\geq$35.4 $\mu$mol/L and 34% when defined as a decline in eGFR $\geq$15 ml/min/1.73 m$^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 1.1–2.3) for composite CV death, recurrent ACS, HF or stroke.

In-hospital death (RR 12.3, 95% CI, 1.8–84.9, $P < .001$). AKI associated with age $> 75$ yrs, LVEF $< 40%$, mechanical ventilation.
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   | N = 118,465    | ADHERE registry          | ADHF            |     | eGFR decrease of at least 15 ml/min/1.73 m² | Use of cardioprotective meds (ACE-I and ARB) decreased with increasing degree of CKD | OR 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 |
| N = 13826              | N total = 7788 | Prospective (ARIC and CHS) | Baseline CVD in 12.9% |     |                          | NA                                  | OR for development of kidney disease 1.54 (CVD versus non-CVD) |
| Ahmed et al., 2007     | N total = 7788 | Retrospective (DIG trial); Propensity-matched study | Ambulatory patients with CHF | eGFR < 60 in 45% |                          | Matched HR: (CKD versus non-CKD) All-cause death 1.71 |
| Campbell et al., 2009  | N = 1102       | Retrospective (single center) | Adult congenital heart disease | eGFR 60–89: 41% | eGFR < 60 in 9% | Matched HR: (CKD versus non-CKD) CV hospitalization 1.17; HF hospitalization 1.08; CV death 1.24; HF death 1.42 |
| Dimopoulos et al., 2008| N = 298        | Retrospective (CATS trial) | 1st anterior wall MI | Change in GFRc | New CHF (RR) | Matched HR: (CKD versus non-CKD) All-cause hospitalization 1.18 |
| Hillege et al., 2003   | N = 1102       |                          |                 |    |                          | All-cause death (HR) eGFR ≥ 90: 1.0; eGFR < 60: 3.25 |

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 m²) in 41% and moderate-severe (eGFR < 60 ml/min per 1.73 m²) 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 ≥ 90, 70–89, and < 70 mL/min/cm², 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 cm² [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 Renocardiac Syndrome (Type 4).

| Study                        | Population (n) | Study type (data source) | CKD stage | Cardiac outcomes (%) | Outcomes (%)                         |
|------------------------------|----------------|--------------------------|-----------|----------------------|--------------------------------------|
| Herzog et al., 1998 [54]     | n = 34,189     | 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      | Retrospective (NHANES II) | eGFR < 70 | 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]         | ≥ 1.1 million  | 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  | 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      | Retrospective (CHARM)     | eGFR < 60 36% | Male 67% | All-cause death (HR) eGFR ≥ 90: 1.0; eGFR 75–89: 1.17; eGFR 60–74: 1.24; eGFR 45–59: 1.54 eGFR < 45: 1.86 |
| McCullough et al., 2007 [58] | n = 37,153     | Retrospective (KEEP)      | eGFR < 60 14.8% | Prevalence CVD (OR): eGFR ≥ 90 1.0; eGFR 75–89 1.14; eGFR 60–74: 1.14; eGFR 45–59: 1.50 eGFR < 45: 1.91 |
| McCullough et al., 2008 [59] | n = 31,417     | 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 a 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 factors, 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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References

[1] “Cardiovascular Disease. 2008,” September, 2008, http://www.americanheart.org/.
[2] J. Coresh, E. Selvin, L. A. Stevens et al., “Prevalence of chronic kidney disease in the United States,” Journal of the American Medical Association, vol. 298, no. 17, pp. 2038–2047, 2007.
[3] R. N. Foley, A. M. Murray, S. Li et al., “Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in the United States medicare population, 1998 to 1999,” Journal of the American Society of Nephrology, vol. 16, no. 2, pp. 489–495, 2005.
[4] C. Ronco, P. McCullough, S. D. Anker et al., “Cardio-renal syndromes: report from the consensus conference of the acute dialysis quality initiative,” European Heart Journal, vol. 31, no. 6, pp. 703–711, 2010.
[5] C. M. Logar, C. A. Herzog, and S. Beddu, “Diagnosis and therapy of coronary artery disease in renal failure, end-stage renal disease, and renal transplant populations,” American Journal of the Medical Sciences, vol. 325, no. 4, pp. 214–227, 2003.
[6] “Annual Data Report Atlas 2007,” NKF, 2008, Accessed September, 2008, http://www.ushrs.org/.
[7] S. Khan and C. A. Amedia, “Economic burden of chronic kidney disease,” Journal of Evaluation in Clinical Practice, vol. 14, no. 3, pp. 422–434, 2008.
[8] S. M. Bagshaw, D. N. Cruz, N. Aspromonte et al., “Epidemiology of cardio-renal syndromes: workshop statements from the 7th ADQI Consensus Conference,” Nephrology Dialysis Transplantation, vol. 25, no. 5, pp. 1406–1416, 2010.
[9] A. Goldberg, H. Hammerman, S. Petcherski et al., “Inhospital and 1-year mortality of patients who develop worsening renal function following acute ST-elevation myocardial infarction,” American Heart Journal, vol. 150, no. 2, pp. 330–337, 2005.
[10] S. S. Gottlieb, W. Abraham, J. Butler et al., “The prognostic importance of different definitions of worsening renal function in congestive heart failure,” Journal of Cardiovascular Failure, vol. 8, no. 3, pp. 136–141, 2002.
[11] H. M. Krumholz, YA. T. Chen, V. Vaccarino et al., “Correlates and impact on outcomes of worsening renal function in patients ≥65 years of age with heart failure,” American Journal of Cardiology, vol. 85, no. 9, pp. 1110–1113, 2000.
[12] B. B. Newsome, D. G. Warnock, W. M. McClellan et al., “Long-term risk of mortality and end-stage renal disease among the elderly after small increases in serum creatinine level during hospitalization for acute myocardial infarction,” Archives of Internal Medicine, vol. 168, no. 6, pp. 609–616, 2008.
[13] C. R. Parikh, S. G. Coca, Y. Wang, E. A. Masoudi, and H. M. Krumholz, “Long-term prognosis of acute kidney injury after acute myocardial infarction,” Archives of Internal Medicine, vol. 168, no. 9, pp. 987–995, 2008.
[14] P. Jose, H. Skali, N. Anavekar et al., “Increase in creatinine and cardiovascular risk in patients with systolic dysfunction after myocardial infarction,” Journal of the American Society of Nephrology, vol. 17, no. 10, pp. 2886–2891, 2006.
[15] A. Nohria, V. Hasselblad, A. Stebbins et al., “Cardio-renal Interactions: insights from the ESCAPE trial,” Journal of the American College of Cardiology, vol. 51, no. 13, pp. 1268–1274, 2008.
[16] D. Logeart, J. Y. Tabet, L. Hittinger et al., “Transient worsening of renal function during hospitalization for acute heart failure alters outcome,” International Journal of Cardiology, vol. 127, no. 2, pp. 228–232, 2008.
[17] M. Metra, S. Nodari, G. Parrinello et al., “Worsening renal function in patients hospitalised for acute heart failure: clinical implications and prognostic significance,” European Journal of Heart Failure, vol. 10, no. 2, pp. 188–195, 2008.
[18] D. Aronson and A. J. Burger, “The relationship between transient and persistent worsening renal function and mortality in patients with acute decompensated heart failure,” Journal of Cardiac Failure, vol. 16, no. 7, pp. 541–547, 2010.
[19] C. A. Belziti, R. Bagnati, P. Ledesma, N. Vulcano, and S. Fernández, “Worsening renal function in patients admitted with acute decompensated heart failure: incidence, risk factors and prognostic implications,” Revista Espanola de Cardiologia, vol. 63, no. 3, pp. 294–302, 2010.
[20] R. D. Kociol, M. A. Greiner, B. G. Hammill et al., “Long-term outcomes of medicare beneficiaries with worsening renal function during hospitalization for heart failure,” American Journal of Cardiology, vol. 105, no. 12, pp. 1786–1793, 2010.
[21] A. Goldberg, E. Kogan, H. Hammerman, W. Markiewicz, and D. Aronson, “The impact of transient and persistent acute kidney injury on long-term outcomes after acute myocardial infarction,” Kidney International, vol. 76, no. 8, pp. 900–906, 2009.
[22] L. M. Mielniczuk, M. A. Pfeffer, E. F. Lewis et al., “Acute decline in renal function, inflammation, and cardiovascular risk after an acute coronary syndrome,” Clinical Journal of the American Society of Nephrology, vol. 4, no. 11, pp. 1811–1817, 2009.
[23] A. Anzai, T. Anzai, K. Naito et al., “Prognostic significance of acute kidney injury after reperfused ST-elevation myocardial infarction: synergistic acceleration of renal dysfunction and left ventricular remodeling,” Journal of Cardiovascular Failure, vol. 16, no. 5, pp. 381–389, 2010.
[24] G. Marenzi, E. Assanelli, J. Campodonico et al., “Acute kidney injury in ST-segment elevation acute myocardial infarction complicated by cardiogenic shock at admission,” Critical Care Medicine, vol. 38, no. 2, pp. 438–444, 2010.
[25] M. R. Cowie, M. Komajda, T. Murray-Thomas, J. Underwood, and B. Ticho, “Prevalence and impact of worsening renal function in patients hospitalized with decompensated heart failure: results of the prospective outcomes study in heart failure (POSH),” European Heart Journal, vol. 27, no. 10, pp. 1216–1222, 2006.
[26] H. M. Krumholz, E. M. Parent, N. Tu et al., “Readmission after hospitalization for congestive heart failure among medicare beneficiaries,” Archives of Internal Medicine, vol. 157, no. 1, pp. 99–104, 1997.
[27] G. L. Smith, V. Vaccarino, M. Kosiborod et al., “Worsening renal function: what is a clinically meaningful change in creatinine during hospitalization with heart failure?” Journal of Cardiovascular Failure, vol. 9, no. 1, pp. 13–25, 2003.
[28] R. Latchamsetty, J. Fang, E. Klein-Rogers et al., “Prognostic value of transient and sustained increase in in-hospital creatinine on outcomes of patients admitted with acute coronary
syndromes,” *American Journal of Cardiology*, vol. 99, no. 7, pp. 939–942, 2007.

[29] N. A. Khan, I. Ma, C. R. Thompson et al., “Kidney function and mortality among patients with left ventricular systolic dysfunction,” *Journal of the American Society of Nephrology*, vol. 17, no. 1, pp. 244–253, 2006.

[30] D. Aronson, M. A. Mittleman, and A. J. Burger, “Elevated blood urea nitrogen level as a predictor of mortality in patients admitted for decompensated heart failure,” *American Journal of Medicine*, vol. 116, no. 7, pp. 466–473, 2004.

[31] J. F. Price, A. R. Mott, H. A. Dickerson et al., “Worsening renal function in children hospitalized with decompensated heart failure: evidence for a pediatric cardiorenal syndrome?” *Pediatric Critical Care Medicine*, vol. 9, no. 3, pp. 279–284, 2008.

[32] R. de Silva, N. P. Nikitin, K. K. A. Witte et al., “Incidence of renal dysfunction over 6 months in patients with chronic heart failure due to left ventricular systolic dysfunction: contributing factors and relationship to prognosis,” *European Heart Journal*, vol. 27, no. 5, pp. 569–581, 2006.

[33] K. Damman, G. Navis, T. D. I. Smilde et al., “Decreased cardiac output, venous congestion and the association with renal impairment in patients with cardiac dysfunction,” *European Journal of Heart Failure*, vol. 9, no. 9, pp. 872–878, 2007.

[34] W. Mullens, Z. Abrahams, G. S. Francis et al., “Importance of venous congestion for worsening of renal function in advanced decompensated heart failure,” *Journal of the American College of Cardiology*, vol. 53, no. 7, pp. 589–596, 2009.

[35] T. D. I. Smilde, H. L. Hillege, G. Navis, F. Boomsma, D. de Zeeuw, and D. J. Van Veldhuisen, “Impaired renal function in patients with ischemic and nonischemic chronic heart failure: association with neurohormonal activation and survival,” *American Heart Journal*, vol. 148, no. 1, pp. 165–172, 2004.

[36] D. Rusinaru, O. Buicuc, D. Houpe, and C. Tribouilloy, “Renal function and long-term survival after hospital discharge in heart failure with preserved ejection fraction,” *International Journal of Cardiology*, 2009.

[37] A. Aghel, K. Shrestha, W. Mullens, A. Borowski, and W. H. W. Tang, “Serum neutrophil gelatinase-associated lipocalin (NGAL) in predicting worsening renal function in acute decompensated heart failure,” *Journal of Cardiac Failure*, vol. 16, no. 1, pp. 49–54, 2010.

[38] R. Pfister, J. Muller-Ehmsen, J. Hagemeister, M. Hellmich, E. Erdmann, and C. A. Schneider, “NT-pro-BNP predicts worsening renal function in patients with chronic systolic heart failure (NT-pro-BNP and renal function),” *Internal Medicine Journal*. In press.

[39] J. T. Heywood, G. C. Fornarow, M. R. Costanzo, V. S. Mathur, J. R. Wigneswaran, and J. Wynne, “High prevalence of renal dysfunction and its impact on outcome in 118,465 patients hospitalized with acute decompensated heart failure: a report from the ADHERE Database,” *Journal of Cardiac Failure*, vol. 13, no. 6, pp. 422–430, 2007.

[40] E. F. Elsayed, H. Tighiouart, J. Griffith et al., “Cardiovascular disease and subsequent kidney disease,” *Archives of Internal Medicine*, vol. 167, no. 11, pp. 1130–1136, 2007.

[41] A. Ahmed, M. W. Rich, P. W. Sanders et al., “Chronic kidney disease associated mortality in diastolic versus systolic heart failure: a propensity matched study,” *American Journal of Cardiology*, vol. 99, no. 3, pp. 393–398, 2007.

[42] R. C. Campbell, X. Sui, G. Filippatos et al., “Association of chronic kidney disease with outcomes in chronic heart failure: a propensity-matched study,” *Nephrology Dialysis Transplantation*, vol. 24, no. 1, pp. 186–193, 2009.

[43] K. Dimopoulos, G. P. Diller, E. Koltsida et al., “Prevalence, predictors, and prognostic value of renal dysfunction in adults with congenital heart disease,” *Circulation*, vol. 117, no. 18, pp. 2320–2328, 2008.

[44] H. L. Hillege, W. H. Van Gilst, D. J. Van Veldhuisen et al., “Accelerated decline and prognostic impact of renal function after myocardial infarction and the benefits of ACE inhibition: the CATS randomized trial,” *European Heart Journal*, vol. 24, no. 5, pp. 412–420, 2003.

[45] U. D. Patel, M. A. Greiner, G. C. Fonarow, H. Phatak, A. F. Hernandez, and L. H. Curtis, “Associations between worsening renal function and 30-day outcomes among Medicare beneficiaries hospitalized with heart failure,” *American Heart Journal*, vol. 160, no. 1, pp. 132–138.e1, 2010.

[46] K. Hebért, A. Dias, M. C. Delgado et al., “Epidemiology and survival of the five stages of chronic kidney disease in a systolic heart failure population,” *European Journal of Heart Failure*, vol. 12, no. 8, pp. 861–865, 2010.

[47] J. Inatomi, K. Matsuoka, R. Fujimaru, A. Nakagawa, and K. Iijima, “Mechanisms of development and progression of cyanotic nephropathy,” *Pediatric Nephrology*, vol. 21, no. 10, pp. 1440–1445, 2006.

[48] P. I. Agras, M. Derbent, F. Ozcan et al., “Effect of congenital heart disease on renal function in childhood,” *Nephron-Physiology*, vol. 99, no. 1, pp. p10–p15, 2005.

[49] P. A. McCullough, R. Wolyin, L. L. Rocher, R. N. Levin, and W. W. O’Neill, “Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality,” *American Journal of Medicine*, vol. 103, no. 5, pp. 368–375, 1997.

[50] L. Gruberg, G. S. Mintz, R. Mehran et al., “The prognostic implications of further renal function deterioration within 48 h of interventional coronary procedures in patients with pre-existent chronic renal insufficiency,” *Journal of the American College of Cardiology*, vol. 36, no. 5, pp. 1542–1548, 2000.

[51] C. S. Rihal, S. C. Textor, D. E. Grill et al., “Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention,” *Circulation*, vol. 105, no. 19, pp. 2259–2264, 2002.

[52] S. D. Weissbord, M. K. Mor, A. L. Resnick et al., “Prevention, incidence, and outcomes of contrast-induced acute kidney injury,” *Archives of Internal Medicine*, vol. 168, no. 12, pp. 1325–1332, 2008.

[53] G. Marenzi, G. Lauri, J. Campodónico et al., “Comparison of two hemofiltration protocols for prevention of contrast-induced nephropathy in high-risk patients,” *American Journal of Medicine*, vol. 119, no. 2, pp. 155–162, 2006.

[54] C. A. Herzog, J. Z. Ma, and A. J. Collins, “Poor long-term survival after acute myocardial infarction among patients on long-term dialysis,” *New England Journal of Medicine*, vol. 339, no. 12, pp. 799–805, 1998.

[55] P. Munter, J. He, L. Hamm, C. Loria, and P. K. Whelton, “Renal insufficiency and subsequent death resulting from cardiovascular disease in the United States,” *Journal of the American Society of Nephrology*, vol. 13, no. 3, pp. 745–753, 2002.

[56] A. S. Go, G. M. Chertow, D. Fan, C. E. McCulloch, and C. Y. Hsu, “Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization,” *New England Journal of Medicine*, vol. 351, no. 13, pp. 1296–1305, 2004.

[57] H. L. Hillege, D. Nitsch, M. A. Pfeffer et al., “Renal function as a predictor of outcome in a broad spectrum of patients with heart failure,” *Circulation*, vol. 113, no. 5, pp. 671–678, 2006.
[58] P. A. McCullough, C. T. Jurkovitz, P. E. Pergola et al., "Independent components of chronic kidney disease as a cardiovascular risk state: results from the Kidney Early Evaluation Program (KEEP)," *Archives of Internal Medicine*, vol. 167, no. 11, pp. 1122–1129, 2007.

[59] P. A. McCullough, S. Li, C. T. Jurkovitz et al., "Chronic kidney disease, prevalence of premature cardiovascular disease, and relationship to short-term mortality," *American Heart Journal*, vol. 156, no. 2, pp. 277–283, 2008.

[60] A. K. Cheung, M. J. Sarnak, G. Yan et al., "Cardiac diseases in maintenance hemodialysis patients: results of the HEMO Study," *Kidney International*, vol. 65, no. 6, pp. 2380–2389, 2004.

[61] B. F. Cullerton, M. G. Larson, P. W. F. Wilson, J. C. Evans, P. S. Parfrey, and D. Levy, "Cardiovascular disease and mortality in a community-based cohort with mild renal insufficiency," *Kidney International*, vol. 56, no. 6, pp. 2214–2219, 1999.

[62] P. A. McCullough, S. Li, C. T. Jurkovitz et al., "CKD and cardiovascular disease in screened high-risk volunteer and general populations: the Kidney Early Evaluation Program (KEEP) and the National Health and Nutrition Examination Survey (NHANES) 1999–2004," *American Journal of Kidney Diseases*, vol. 51, no. 4, pp. S38–S45, 2008.

[63] A. El-Menyar, M. Zubaid, K. Sulaiman et al., "In-hospital major clinical outcomes in patients with chronic renal insufficiency presenting with acute coronary syndrome: data from a registry of 8176 patients," *Mayo Clinic Proceedings*, vol. 85, no. 4, pp. 332–340, 2010.

[64] J. O. Burton, H. J. Jefferies, N. M. Selby, and C. W. McIntyre, "Hemodialysis-induced repetitive myocardial injury results in global and segmental reduction in systolic cardiac function," *Clinical Journal of the American Society of Nephrology*, vol. 4, no. 12, pp. 1925–1931, 2009.

[65] C. A. Herzog, "Dismal long-term survival of dialysis patients after acute myocardial infarction: can we alter the outcome?" *Nephrology Dialysis Transplantation*, vol. 17, no. 1, pp. 7–10, 2002.

[66] J. Törning, K. Amann, E. Ritz, C. Nichols, M. Zeier, and G. Mall, "Arteriolar wall thickening, capillary rarefaction and interstitial fibrosis in the heart of rats with renal failure: the effects of ramipril, nifedipine and moxonidine," *Journal of the American Society of Nephrology*, vol. 7, no. 5, pp. 667–675, 1996.

[67] M. W. Yerkey, S. J. Kernis, B. A. Franklin, K. R. Sandberg, and P. A. McCullough, "Renal dysfunction and acceleration of coronary disease," *Heart*, vol. 90, no. 8, pp. 961–966, 2004.

[68] R. S. Wright, G. S. Reeder, C. A. Herzog et al., "Acute myocardial infarction and renal dysfunction: a high-risk combination," *Annals of Internal Medicine*, vol. 137, no. 7, pp. 563–570, 2002.

[69] J. N. Beattie, S. S. Soman, K. R. Sandberg et al., "Determinants of mortality after myocardial infarction in patients with advanced renal dysfunction," *American Journal of Kidney Diseases*, vol. 37, no. 6, pp. 1191–1200, 2001.

[70] A. K. Berger, S. Duval, and H. M. Krumholz, "Aspirin, beta-blocker, and angiotensin-converting enzyme inhibitor therapy in patients with end-stage renal disease and an acute myocardial infarction," *Journal of the American College of Cardiology*, vol. 42, no. 2, pp. 201–208, 2003.

[71] J. J. Grantham, "Autosomal dominant polycystic kidney disease," *New England Journal of Medicine*, vol. 359, no. 14, pp. 1477–1485, 2008.

[72] W. E. Braun, "Autosomal dominant polycystic kidney disease: emerging concepts of pathogenesis and new treatments," *Cleveland Clinic Journal of Medicine*, vol. 76, no. 2, pp. 97–104, 2009.

[73] S. M. Bagshaw, C. George, and R. Bellomo, "Early acute kidney injury and sepsis: a multicentre evaluation," *Critical Care*, vol. 12, no. 2, article no. R47, 2008.

[74] S. M. Bagshaw, S. Uchino, R. Bellomo et al., "Septic acute kidney injury in critically ill patients: clinical characteristics and outcomes," *Clinical Journal of the American Society of Nephrology*, vol. 2, no. 3, pp. 431–439, 2007.

[75] S. M. Bagshaw, S. Lapinsky, S. Dial et al., "Acute kidney injury in septic shock: clinical outcomes and impact of duration of hypotension prior to initiation of antimicrobial therapy," *Intensive Care Medicine*, vol. 35, no. 5, pp. 871–881, 2009.

[76] J. Charpentier, C. E. Luyt, Y. Fulla et al., "Brain natriuretic peptide: a marker of myocardial dysfunction and prognosis during severe sepsis," *Critical Care Medicine*, vol. 32, no. 3, pp. 660–665, 2004.

[77] P. Ammann, T. Fehr, E. Minder, C. Günter, and O. Bertel, "Elevation of troponin I in sepsis and septic shock," *Intensive Care Medicine*, vol. 27, no. 6, pp. 965–969, 2001.