ABSTRACT
Cardiorenal syndrome (CRS) is a complex spiral of vascular disease entity, in which affliction of one organ (kidney) may adversely impact the functioning of the other (heart). Recent consensus conference has clearly defined its various types and pathophysiology. Improved survival, cardiovascular risk factors (diabetes, hypertension, dyslipidemia), diagnostic and therapeutic intervention [contrast agent, improper diuretic usage, nonsteroidal anti-inflammatory drugs (NSAIDs)] are some contributors in its causation. A proper understanding of its mechanism and subsequent individualized approach can stall its progressive spiral. This chapter addresses preventive and established therapeutic strategies such as diuretics and inotropes, in the CRS as well as novel therapies that hold promise, such as arginine vasopressin antagonists, adenosine A1 receptor antagonists and ultrafiltration.

INTRODUCTION
Cardiorenal syndrome is defined as “disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other”.

The coexistence of cardiac and renal disease significantly increases mortality, morbidity, complexity and cost of care, and carries an extremely bad prognosis. The exact cause of deterioration of kidney function and the mechanism underlying this interaction are complex, multifactorial in nature, and still not completely understood. Renal dysfunction is one of the most important comorbidities in heart failure. Reduced estimated glomerular filtration rate (eGFR) seems to be a potent predictor of cardiovascular complications and mortality. Patients with renal dysfunction have a significantly increased risk of developing an adverse outcome after acute myocardial infarction (AMI).

The most common underlying risk factors that account for renal dysfunction in the setting of heart failure or cardiac dysfunction include hypertension, diabetes mellitus, severe atherosclerotic disease, elderly age and a prior history of renal insufficiency or heart failure.

CARDIORENOAL CONNECTION
Both heart and the kidneys are richly vascular (the kidneys are more vascular than the heart) and both organs are supplied by sympathetic and parasympathetic innervations. These two organs act in tandem to regulate blood pressure, vascular tone, diuresis, natriuresis, intravascular volume homeostasis, peripheral tissue perfusion and oxygenation. They have endocrine functions with interdependent physiological hormonal actions regulated by arterial natriuretic peptide, a vasodilator secreted from the heart and renin-angiotensin-aldosterone system (RAAS). Also, vitamin D3, erythropoietin and renalse are all secreted from the kidneys, and are capable of cellular and humoral signaling. Dysfunction of either of the two organs can cause dysfunction of the other (Figures 1 and 2). Changes in the RAAS, the imbalance between nitric oxide (NO) and reactive oxygen species (ROS), the sympathetic nervous system and inflammation are the cardiorenal connectors to develop CRS.

EPIDEMIOLOGY
Heart failure is a common chronic condition affecting 2% of the adult population and resulting in over 1 million annual admissions, making it the leading cause of hospitalization in both developing and developed world adults over the age of 65 years. Patients with chronic kidney disease (CKD) have a greater risk of cardiovascular disease (CVD) mortality ranging from 15 to 30 times that of healthy individuals, with an associated disproportionate use of healthcare resources.

PATHOPHYSIOLOGY
Three main factors have been implemented: (1) low-cardiac output; (2) elevation of both intra-abdominal and central venous pressures and (3) neurohormonal and inflammatory activation.

DIAGNOSIS
Early identification of worsening kidney function is essential for early treatment of CRS. Use of biomarkers that become detectable before the traditional tests for kidney function, including GFR or serum creatinine have made to easier. Biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL), N-acetyl-β-D-glucosaminidase (NAG) and kidney injury molecule 1 (KIM-1) implicated in tubulointerstitial damage are being used to identify acute kidney injury (AKI). Serum cystatin C is elevated earlier than creatinine. Furthermore, while cystatin C in the serum is a marker of reduced glomerular filtration, urinary cystatin C is a marker of tubular dysfunction. Other biomarkers that have proven useful include B-type natriuretic peptide (BNP), interleukin-18 (IL-18) and fatty acid-binding protein (FABP). Tests for volume status and end-organ perfusion are also useful in the diagnosis of CRS. Urine sediment examination should be performed in differentiating CRS from other causes of AKI by excluding pathologic cells, casts or crystals. Hyponatremia, when present, may indicate excess antidiuretic hormone (ADH) and portend an overall poor prognosis.
One study proposed that patients with renal dysfunction had a significantly increased risk (almost 4 times) of developing an adverse outcome (recurrent acute coronary syndromes, revascularization, left ventricular failure, death) after AMI. This entity has specific treatment and prevention strategies.

Preventive Approaches
The basic principles include avoidance of volume depletion, removal of superimposed renal toxic agents (NSAIDs agents, aminoglycosides), minimization of the toxic exposure (iodinated contrast, time on cardiopulmonary bypass) and possibly, the use of antioxidant agents such as N-acetylcysteine and BNP in the perioperative period after cardiac surgery. Use of continuous renal replacement therapy (CRRT) provides three important protective mechanisms that cannot be achieved pharmacologically as follows: (1) it ensures euvolemia and avoids hypo- or hypervolemia; (2) it provides sodium and solute (nitrogenous waste products) removal and (3) by both mechanisms above, it may work to avoid both passive renal congestion and a toxic environment for the kidneys.

Management
Type I CRS appears in the setting of ADHF or cardiogenic shock for a number of reasons, with hemodynamic derangements ranging from acute pulmonary edema with hypertension through severe peripheral fluid overload to cardiogenic shock and hypotension. Table 2 summarizes some practical recommendations for the management of ADHF patients with Type I CRS. The goal of diuretic use should be to deplete the extracellular fluid volume at a rate that allows adequate time for intravascular refilling from the interstitium. To achieve adequate diuresis, infusions of loop diuretics have been demonstrated to have greater efficacy than intermittent dosing.

If kidney function continues to worsen, blockade of the RAAS may be a contributing factor, necessitating withholding or delaying the introduction of angiotensin-converting-enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) in order to maintain the GFR.

For Type I CRS patients with preserved or elevated blood pressure, vasodilators such as nitroglycerin and nitroprusside are often used to relieve symptoms and improve hemodynamics. When patients have low blood pressure and poor renal perfusion, positive inotropes such as dobutamine or phosphodiesterase inhibitors may be required.

CARDIORENAL SYNDROME: CLASSIFICATION AND MANAGEMENT
The CRS was classified into five categories, according to the underlying etiologies and the nature of concomitant cardiac and renal dysfunction (Table 1).

Acute Cardiorenal Syndrome: Type I
This appears to be a syndrome of worsening renal function that frequently complicates hospitalized patients with acute decompensated heart failure (ADHF) and acute coronary syndrome.
Acute Renocardiac Syndrome: Type III

Although AKI is documented as an important cause of acute heart disorder, the pathophysiological mechanisms likely go beyond simple volume overload and hypertension, and the recent consensus definition for AKI will aid in the investigation and analysis of epidemiologic data. The development of new biomarkers, and the study of prevention and management strategies in AKI following radiocontrast or cardiac surgery, will increase our knowledge of this syndrome.

Preventive Approaches

The major management principle concerning this syndrome is intra- and extravascular volume control with either use of diuretics and forms of extracorporeal volume and solute removal (CRRT, ultrafiltration, hemodialysis).

Management

In Type III CRS, AKI occurs as a primary event (e.g. acute glomerulonephitis) or secondary event (e.g. radiocontrast, exogenous or endogenous nephrotoxins, postsurgical, etc.) and cardiac dysfunction is a common and often times fatal sequela. A common example of Type III CRS occurring in the hospital setting is contrast nephropathy, particularly in patients undergoing coronary and other angiographic procedures who have risk factors such as pre-existing CKD, diabetes, older age or volume contraction. In these susceptible populations, prevention may provide the best opportunity to “treat” or avoid Type III CRS. Many potential preventive strategies have been studied, including parenteral hydration (hypotonic or isotonic saline or bicarbonate), diuretics, mannitol, natriuretic peptides, dopamine, fenoldopam, theophylline and N-acetylcysteine.

Treatment of primary kidney diseases such as acute glomerulonephritis or kidney allograft rejection may potentially lessen the risk of Type III CRS, but this has not been systematically studied. Furthermore, many immunosuppressive drugs used for such treatment have adverse effects on the cardiovascular system through their effects on blood pressure, lipids and glucose metabolism.

TABLE 1 | Classification of cardiorenal syndrome proposed by Ronco et al.

<table>
<thead>
<tr>
<th>Type</th>
<th>Name</th>
<th>Mechanism</th>
<th>Clinical conditions</th>
<th>Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>Acute cardiorenal syndrome</td>
<td>Abrupt worsening of cardiac function leading to acute kidney injury</td>
<td>Acute cardiacogenic shock and acutely decompensated congestive heart failure</td>
<td>ET-1, troponin, CPK-MB</td>
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<tr>
<td>Type II</td>
<td>Chronic cardiorenal syndrome</td>
<td>Chronic abnormalities in cardiac function causing progressive and potentially permanent kidney disease</td>
<td>Chronic congestive heart failure</td>
<td>ET-1, BNP</td>
</tr>
<tr>
<td>Type III</td>
<td>Acute renocardiac syndrome</td>
<td>Abrupt worsening of kidney function causing acute cardiac disorder</td>
<td>Acute kidney ischemia and glomerulonephritis</td>
<td>TNF-alfa, IL-1, IL-6, IL-8</td>
</tr>
<tr>
<td>Type IV</td>
<td>Chronic renocardiac syndrome</td>
<td>Chronic kidney disease contributing to decline in cardiac function</td>
<td>Chronic glomerular and interstitial disease</td>
<td>PTH, CPP product, cystatin C</td>
</tr>
<tr>
<td>Type V</td>
<td>Secondary cardiorenal syndrome</td>
<td>Systemic condition causing both cardiac and kidney dysfunction</td>
<td>Diabetes mellitus, sepsis</td>
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</tbody>
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Abbreviations: ET-1, Endothelin-1; CPK-MB, Creatine phosphokinase-MB; BNP, B-type natriuretic peptide; TNF, Tumor-necrosis factor; IL, Interleukin; PTH, Parathyroid hormone; CPP, Calcium-phosphate product; Ellipses indicate not applicable.

TABLE 2 | Practical recommendations for the management of acute decompensated heart failure (ADHF) patients with cardiorenal syndrome (CRS) (Katerina Koniari et al.)

- Restrict fluid and sodium intake
- Increase furosemide dose
- Use continuous intravenous furosemide
- Add thiazides or metolazone
- Add renoprotective dopamine at 2–3 mcg/kg/min
- Add inotrope or vasodilator (according to systolic blood pressure)
- Start ultrafiltration
- Insert intra-aortic balloon pump
- Insert another device

Chronic Cardiorenal Syndrome: Type II

This subtype is a separate entity from acute CRS as it indicates a more chronic state of kidney disease complicating chronic heart disease. This is an exceptionally common problem. For instance, in patients hospitalized with congestive heart failure (CHF), approximately 63% meet the kidney disease outcomes quality initiative (K/DOQI) definition of stages 3–5 CKD (eGFR < 60 mL/min/1.73 m²). Preventive Approaches

Pharmacologic therapies that have been beneficial for chronic CVD may have been either neutral or favorable to the kidneys including use of RAAS antagonists, beta-adrenergic blocking agents and statins. Furthermore, other strategies including glycemic control in diabetes and blood pressure control in those with hypertension. Management

Interruption of the RAAS is the primary aim in the management of Type II CRS. However, RAAS blockade can lead to significant decrease in kidney function and/or elevated potassium. However, creatinine tended to stabilize, and in many instances, improved over the course of the study. In terms of aldosterone blockade, drugs such as spironolactone and eplerenone are important adjuncts to therapy in patients with severe heart failure. Both CHF and CKD are associated with anemia, which is commonly treated with erythropoiesis-stimulating agents. Furthermore, the action of erythropoietin in the heart may reduce apoptosis, fibrosis and inflammation. Hence, there has been intense interest in using erythropoiesis-stimulating agents in heart failure patients.
**Nephrology**

**Chronic Renocardiac Syndrome: Type IV**

A large body of evidence has accumulated demonstrating the graded and independent association between level of CKD and adverse cardiac outcomes.

**Preventive Approaches**

Optimal treatment of CKD with blood pressure and glycemic control, RAAS blockers and disease-specific therapies, when indicated, are the best means of preventing this syndrome. Morbidities of CKD, including bone and mineral disorder and anemia, should be managed according to CKD guidelines.

**Management**

The management of Type IV CRS is multifaceted focusing on the decline of cardiovascular risk factors and complications common to CKD patients. These include, but are not limited to, anemia, hypertension, altered bone and mineral metabolism, dyslipidemia, smoking, albuminuria and malnutrition. Several therapies targeting such uremic complications as anemia, homocysteine, calcium-phosphate product and hyperparathyroidism are supported by observational studies demonstrating the association between adverse cardiovascular events and these conditions.

**Secondary Cardiorenal Syndromes: Type V**

This subtype does not have a primary and secondary organ dysfunctions, situations do arise where both organs simultaneously are targeted by systemic illnesses, either acute or chronic. Examples include sepsis, systemic lupus erythematosus (SLE), amyloidosis and diabetes mellitus.

**Preventive Approaches**

There are no proven methods to prevent or ameliorate this form of CRSs at this time. Supportive care with a judicious intravenous fluid approach and the use of pressor agents as needed to avoid hypotension are reasonable but cannot be expected to avoid AKI or cardiac damage.

**Management**

Examples of Type V CRS include a heterogeneous group of disorders such as sepsis, SLE, amyloidosis and diabetes mellitus. It is difficult to formulate a treatment strategy to encompass all of these disorders, but more important is the recognition that injury to one organ is likely to influence or injure the other organ and vice versa. Therapies directed to the improvement in function of one organ need to consider the interaction with, and role of the other. As sepsis is one of the more common acute disorders that involves multiple organs, and often causes co-dysfunction of kidneys and heart. Recognition of Type V CRS as an entity in sepsis and other systemic disorders will allow further research into the signaling and mechanisms of injury, and allow for the development of rational and efficient therapies.

**FUTURE DIRECTIONS IN TREATMENT OF CARDIORENAL SYNDROME**

Potentially promising pharmacological approaches include selective adenosine A1 receptor blockers, which have a variety of effects on intrarenal hemodynamics and tubular function, and vasopressin antagonists (V2 receptor antagonists “vaptans”, e.g. conivaptan and tolvaptan). Adenosine can lower cortical blood flow, resulting in antinatriuretic responses. A1 receptor antagonists have been shown to cause diuresis and natriuresis while minimally affecting potassium excretion or glomerular filtration. Other interventions include the earlier use of dialysis and ultrafiltration, and ultimately, left ventricular assist devices to manage these patients effectively, at least in the short-term.

**CONCLUSION**

Cardiorenal syndrome is an interdependent involvement of both the heart and the kidney in a spiral fashion. Decrease in GFR or creatinine clearance in patients with decompensated heart failure involves longer hospital stays, higher hospital costs, higher in-hospital mortality rates and more readmissions but still the prognosis is grave. Earlier use of slow high-dose intravenous diuretics, dialysis with ultrafiltration for treatment of congestion, inotropes and left ventricular assistant device to stabilize the hemodynamics and maintenance of the renal perfusion is the vital component for a short period of time, which is a clinical challenge of initial management. There is no selective pharmacological therapy available to directly influence the four cardiorenal connection (balance between NO and ROS, RAAS, inflammation and the sympathetic nervous system), other than ACEI and aldosterone inhibitors to block the RAAS and inhibit oxidative stress and inflammation. Postulation to intervene all these connectors may stop the cascade of cardiorenal connection to prevent severe CRS.

**REFERENCES**