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Cardiorenal Syndromes: Advances in Determining Diagnosis, Prognosis, and Therapy

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Abstract

The term cardiorenal syndrome (CRS) implies acute or chronic injury to the heart and kidneys that often involves a temporal sequence of disease initiation and progression. The classification of CRS is divided into five subtypes. Types 1 and 2 involve acute and chronic cardiovascular disease (CVD) scenarios leading to acute kidney injury (AKI) or accelerated chronic kidney disease (CKD). Types 3 and 4, describe AKI and CKD, respectively, leading primarily to heart failure, although, it is possible that acute coronary syndromes, stroke, and arrhythmias could be CVD outcomes in these forms of CRS. Finally, CRS type 5 describes a systemic insult to both heart and the kidneys, such as sepsis, where both organs are injured simultaneously in persons with previously normal heart and kidney function at baseline. This manuscript will summarize key issues and future opportunities in challenging patients with CRS. Because most CRS occur in patients with pre-existing myocardial disease or chronic kidney disease, we will emphasize the chronic condition which puts individuals at risk for acute events. In the setting of a hospitalization, acute CRS can occur which have been consistently associated with inpatient complications, longer lengths of intensive care unit and hospital stay, need for renal replacement therapy, rehospitalization and death. While there are several common diagnostic and therapeutic targets for the heart and kidney, there remains considerable opportunity for both in-vitro diagnostics and medicinal therapy to favorably influence the occurrence and natural history of CRS.

Introduction

The term cardiorenal syndrome (CRS) implies acute or chronic injury to the heart and kidneys that often involves a temporal sequence of disease initiation and progression. The classification of CRS is divided into five subtypes each of which has complicated and poorly understood pathogenetic factors, yet holding promise for research and clinical opportunities to improve patient outcomes (Figure 1). Types 1 and 2 involve acute and chronic cardiovascular disease (CVD) scenarios leading to acute kidney injury (AKI) or accelerated chronic kidney disease (CKD). Types 3 and 4, describe AKI and CKD, respectively, leading primarily to heart failure, although, it is possible that acute coronary syndromes, stroke, and arrhythmias could be CVD outcomes in these forms of CRS. Finally, CRS type 5 describes a systemic insult to both heart and the kidneys, such as sepsis, where both organs are injured simultaneously in persons with previously normal heart and kidney function at baseline. It has been long-recognized that the most significant predictor of cardiovascular outcomes in coronary atherosclerosis and myocardial disease is baseline renal function as reflected by the serum creatinine, blood urea nitrogen, cystatin-C, calculated creatine clearance, and estimated glomerular filtration rate (eGFR) [1-3]. While it is believed that a considerable amount of the association between decreased renal function and cardiovascular outcomes is due to confounding by older age, diabetes, hypertension, and fragility, there remains considerable variability that is likely explained by pathophysiology that involves both organ systems via organ cross-talk [4,5]. Conversely, it has also been well-recognized that a leading cause of mortality among patients with advanced chronic kidney disease (CKD) and end-stage renal disease (ESRD) is cardiovascular disease [6]. Of particular note, patients with significant CKD are more likely to die of cardiovascular disease than reach ESRD and require dialysis. Thus, there has been considerable interest in CRS as an important clinical intersection in which new diagnostic and therapeutic targets may be found. As the majority of acute CRS occur in the setting of pre-existing disease (heart failure or CKD), we will discuss chronic CRS as the set-up for acute CRS.

Chronic Cardiorenal Syndromes

In the schema of five CRS subtypes, the chronic CRS are Type 2

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Cardiorenal Syndrome (CRS) General Definition:
A pathophysiologic disorder of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ

CRS Type I (Acute Cardiorenal Syndrome)
Abrupt worsening of cardiac function (i.e. acute heart failure) leading to acute kidney injury
•Major mechanisms: neurohormonal, abnormal cell signaling, hemodynamic derangements
•Opportunities: identify the ~25% of HF that will develop AKI, test novel drugs/strategies

CRS Type II (Chronic Cardiorenal Syndrome)
Chronic abnormalities in cardiac function (i.e. chronic heart failure) leading to progressive and permanent chronic kidney disease
•Major mechanisms: chronic neurohormonal hyperactivation
•Opportunities: control risk of hyperkalemia and intensify ACEI or ARB, MRA, BB

CRS Type III (Acute Renocardiac Syndrome)
Abrupt worsening of renal function (i.e. AKI) leading to acute cardiac disorder (e.g. acute heart failure, arrhythmia)
•Major mechanisms: acute volume overload, hyperkalemia, acidosis
•Opportunities: Novel drugs/strategies to prevent or treat AKI and improve cardiac outcomes/reduce complications

CRS Type IV (Chronic Renocardiac Syndrome)
Chronic kidney disease (e.g. chronic glomerular disease) contributing to decreased cardiac function, cardiac hypertrophy and/or increased risk of adverse cardiovascular events
•Major mechanisms: chronic pressure and volume overload, uremic cardiomyopathy, metabolic/micronutirent degrangment
•Opportunities: SGLT2 inhibitors, low dose ET-A antagonists, control risk of hyperkalemia and intensify ACEI or ARB, MRA, treat metabolic abnormalities (uric acid, anemia, bone and mineral disorder, micronutrient abnormalities

CRS Type V (Secondary Cardiorenal Syndrome)
Systemic condition (e.g. sepsis) causing both cardiac and renal dysfunction
•Major mechanisms: cytokine storm, danger associated molecular patterns
•Opportunities: acute cyokine reduction, immunomodulation, adavancd life suppport

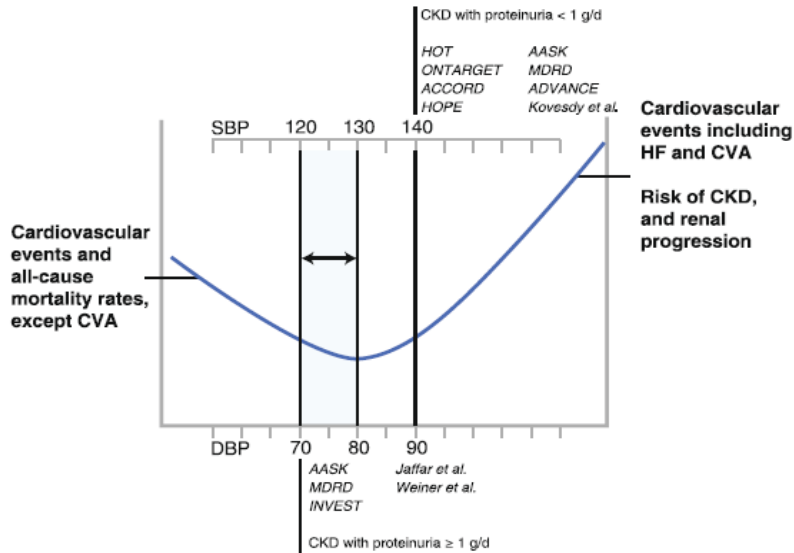**Figure 1:** Classification of five CRS.

Figure 2: U-shaped relationship for treated blood pressure and cardiac and renal outcomes from clinical trials.

(chronic HF leading to progressive CKD) and Type 4 (CKD and its related hemodynamic and metabolic changes leading to myocardial dysfunction and HF). A notable feature of Type 4 CRS is accelerated myocardial and tubulointerstitial fibrosis. Fibrosis in the myocardium is directly related to mechanical dysfunction and arrhythmogenesis (atrial fibrillation and re-entrant ventricular tachycardia resulting in ventricular fibrillation). The most common conditions that lead to chronic CRS are hypertension and diabetes mellitus. While it is possible that diseases without either of these conditions can be present such as polycystic kidney disease, vesiculo-ureteral reflux, or IgA nephropathy, when we discuss chronic CRS we consider either diabetes or hypertension or both to be nearly universally present.

Impact of Blood Pressure Control on the Heart and Kidneys

For many years, systemic blood pressure has been a clinical target in both heart and kidney disease [7,8]. For the reduction in disease progression in both organs, blood pressure control is a cornerstone of management. The cardiovascular outcomes most responsive to

blood pressure control are stroke and heart failure (Figure 2) [9]. Likewise, blood pressure control in CKD is associated with reductions in proteinuria, a slower decline in loss of eGFR, and reduced rates of incident ESRD. Thus a major current therapeutic target for management of chronic CRS is blood pressure with the caveat that for both organs there is a U-shaped relationship with outcomes as illustrated in the Figure 2 [9]. Given the dozens of available agents to treat hypertension, there is little development activity at this time for novel agents that would be of particular or unique benefit in CRS. The National Institutes of Health Systolic Blood Pressure Intervention Trial (SPRINT) will test in 9250 adults over age 50 a strategy of intensive blood pressure control versus standard control on the outcome of first occurrence of a myocardial infarction, acute coronary syndrome, and stroke, heart failure, or CVD death. In this study, there is a pre-specified CKD subgroup would serve as an excellent validation for the event curve presented in Figure 2 [10].

Treatment of Diabetes and Newer Antidiabetic Agents

The control of blood glucose over time as reflected in the hemoglobin A1C has been a mainstay of therapy to slow the progression of CKD (termed "microvascular disease" in trials) and reduce the incidence of binary events such as myocardial infarction or stroke. As a general observation, the impact of glycemic control has a larger benefit on the kidneys than the heart particularly with respect to atherosclerosis and heart failure. In fact, there are particular caveats for the cardiorenal system and treatment of diabetes that are twofold: 1) tight glycemic control that results in hypoglycemia may trigger myocardial infarction and cardiovascular death, 2) certain antidiabetic agents have direct adverse myocardial effects that can either mask ischemia or lead to the development of myocardial dysfunction, fluid overload, and heart failure (sulfonylureas, peroxisome proliferator-activated receptor (PPAR) agonists, and possibly dipeptidyl peptidase 4 (DPP4) inhibitors) [11-13]. We recognize there is considerable controversy around the cardiovascular safety of antidiabetic drugs, but we make the point that if a safety risk exists, it is in patients with CKD for the outcome of heart failure which has been overlooked by regulatory guidance documents and in the design of many clinical trials which have focused on myocardial infarction, stroke, and cardiovascular death. Thus, unlike antihypertensive agents, there is considerable interest in novel anti diabetic agents that could overcome these limitations and more favorably affect patients with chronic CRS. The discovery and development of inhibitors of the sodium-glucose transporter-2 (SGLT) have generated considerable interest in the cardiorenal community. These agents inhibit the tubular reabsorption of sodium and glucose in the proximal tubule and thus enhance losses of both sodium and glucose resulting in lower blood pressure (without a concomitant heart rate increase), and reduced serum glucose and hemoglobin A1C. In addition to alpha-glucosidase inhibitors, SGLT inhibitors (canaglifozin, dapaglifozin, empagliflozin) work to limit the availability of glucose to cells and result in a net loss of glucose containing calories to the body [14]. This creates a scenario favorable to weight loss and improved cardiometabolic status; which along with osmotic dieresis and lower blood pressure may theoretically decrease the risk of developing HF (although this has yet to be formally tested). Clinical trials are underway to evaluate SGLT-2 inhibitors for major cardiac and renal events including myocardial infarction, stroke, cardiovascular death, progression of CKD, and ESRD) [15]. It should be noted that the efficacy of SGLT-2 inhibitors depends on renal filtration in order to clear glucose in the urine, and thus these agents would have declining efficacy in very low eGFR patients.

Current Medical Therapy for Chronic Myocardial and Renal Disease

In terms of medicinal therapy, several classes of agents have favorable effects on both the heart and the kidneys primarily in the setting of chronic management. It has been long-recognized that agents that antagonize the renin-angiotensin system in general have beneficial effects on both the heart and kidneys including reductions in left ventricular hypertrophy, reductions in heart failure hospitalization and death, and to a lesser extent reductions in myocardial infarction and stroke; and for the kidneys, lessening of proteinuria, and delayed progression of CKD to ESRD. In general, angiotensin-converting enzyme inhibitors (ACEI) have the most solid base of evidence for benefit in heart disease as well as kidney disease. For those who ACEI-intolerant, angiotensin II receptor antagonists (ARB) have a clinical role. However, despite early enthusiasm with dual therapy, the use of ACEI and ARB together has resulted in an unfavorable risk/benefit balance with higher rates of acute kidney injury, hyperkalemia, and hypotension [16]. The additional use of direct renin-inhibitors has also not been shown to have added benefit over ACEI or ARB alone [17]. The chronic use of beta-adrenergic receptor antagonists and mineralocorticoid receptor antagonists (MRA) in general has been associated with improved cardiorenal outcomes provided they are tolerated and free of toxicities including hypotension and hyperkalemia [18]. It is reasonable to infer that the true potential impact of MRA use in patients with significant CKD has not been realized because of dose limiting or prohibiting effects of hyperkalemia [19]. Thus, as indicated below, novel agents to control potassium could indirectly allow a greater use of both RAAS-i and MRAs with potential positive impact on the outcomes of patients with CKD (particularly when combined with HF) in the community.

Therapeutic Targets Beyond Blood Pressure and Glucose

Considerable efforts have been undertaken to understand the range of metabolic perturbations that occur in CKD and evaluate their modification in terms of both renal and cardiac outcomes. Many of these factors (acidosis, iron, vitamin D, calcium, phosphorus, parathyroid hormone, fibroblast growth factors, erythropoietin, anemia, uric acid, oxidative stress, etc.) have their own set of confounders that can range from diet, lifestyle, socioeconomic status, to complex biologic interplays and medication effects [20]. Needless to say, it has been difficult to identify a single causative factor for incident or accelerated cardiovascular disease in CKD patients. Clinical trials have worked through many of these factors in search of fulfilling Koch's hypothesis, that is, change the putative factor and influence the outcome. To date, modifications of a factor such as hemoglobin, parathyroid hormone, or oxidative stress have resulted in no demonstrable benefit, direct toxicity, or off-target deleterious effects leading to cessation of clinical development. Importantly, most of these trials have broadly included patients with CKD with little profiling of populations or strategic use of therapies. Thus, important subgroups for benefit or harm may have been missed. In addition, there have been little or no attempts at mitigating risk for toxicities. For example, in clinical trials of erythrocyte simulating agents (erythropoietin, darbepoetin) there was no effort to exclude patients with resistance to these agents, and as a result patients were subjected to supraphysiologic doses of these agents which had cardiovascular toxicity (e.g. hypertension, stroke, heart failure) [21]. In the case of studies on anemia, the practicing community has been left with considerable confusion over the cause of the adverse outcome: was it secondary to raising hemoglobin or supraphysiologic dosing of the study drugs. Another notable development was the attempt to modify

detoxification enzymes and reduce oxidative stress with bardoxolone, which improved eGFR but in a large clinical trial precipitated acutely decompensated heart failure and related mortality [22]. In this example, there were insufficient efforts to mitigate the potential risks of fluid overload [23]. As a result, many CKD trials exclude patients with a prior history of HF or elevations of BNP in order to mitigate against potential cardiotoxicity [24].

Despite these prior setbacks, the future remains bright in terms of exploration of treatments for CKD that would reduce the rate of progression and at the same time lessen the burden of cardiovascular disease. Among hopeful strategies are the use of novel oral and intravenous iron preparations, inhibitors of hypoxia-inducible factor prolyl hydroxylase prolyase, endothelin receptor antagonists, xanthine oxidase inhibitors, treatment of acidosis, designer natriuretic peptides and anti-fibrotic agents including partial inhibitors of galectin-3. Two particularly advanced areas of therapies include newer antidiabetic agents and potassium binders.

Current *in vitro* Diagnostic Tests in Chronic Management of Cardiorenal Disease

In terms of in vitro diagnostic tests, it has been appreciated that blood B-type natriuretic peptide (BNP) and NT-terminal proBNP (NT-proBNP) reflect a heart-kidney hormonal system that signals increased wall tension in the cardiac chambers with a message to the kidneys to increase natriuresis, diuresis, and lower blood pressure [25]. In asymptomatic patients with CKD, elevations in BNP are strongly predictive for the future development of HF, and thus are used clinically in risk stratification and in clinical trials of novel CKD treatments for risk mitigation for the development of HF as a serious adverse event [26]. There are now a host of acute and chronic disease markers in cardiorenal disease which are in either clinical use or development that will play a major role in the screening, detection, prognosis, and

management of disease [27]. A list of selected chronic cardiorenal biomarkers is shown given in Table 1. Cardiac blood biomarkers in the chronic setting that reflect accelerated apoptosis and cell turnover include troponin I and T. With the use of super-sensitive assays for these proteins, most patients with CKD have detectable levels and the plasma concentration at steady state is related to increased risk of heart failure hospitalization and death in patients with CKD. Suppressor of tumorigenicity 2 (ST2) is a decoy protein produced by the endothelial lining of the left ventricle and aortic outflow tract that blocks the interleukin-33 (IL-33) receptor on cardiomyocytes and satellite cells and impairs the favorable IL-33 signal to these cells, and thus turns on cellular processes that promote myocyte dysfunction and fibrosis [28]. ST2 appears to be unaffected by reductions in eGFR, although there is evidence that with increase in renal fibrosis, there may be elevations in ST2 levels. Galectin-3 is an animal lectin which is secreted by macrophages in solid organs (heart, kidney, liver) and stimulates fibroblasts to proliferate and secrete procollagen I which is crosslinked to mature collagen fibers in the extracellular matrix. Galectin-3 has been found to be reflective of both cardiac and renal fibrosis and is the first directly pathogenic measurable blood factor in cardiorenal disease [29-31]. All four of these markers (BNP/NT-proBNP, troponin I/T, ST2, and galectin-3) are recommended for use by the most recent American College of Cardiology/American Heart Association Guideline for the diagnosis and management of heart failure [32].

In terms of biomarker guidance in the management of CKD, the reliance on serum creatinine and urine albumin or protein as markers of disease progression has been both a guiding principal but also a retardant for breakthrough treatments. A doubling of serum creatinine which is a common endpoint in CKD trials requires a 57% reduction in eGFR [33]. Thus to witness an "important clinical signal" is to observe greater than half of organ function to be lost which cannot recover. This paradigm has led to stagnation in clinical development of agents to reduce the progression of CKD. A recent proposal that

Biomarkers	Current Status	Biological and Physiological Properties	Measurable in Plasma, Serum or Blood	Measurable in Urine	*In Vitro* Diagnostic Target§	Potential Clinical Utility and Guided Therapeutic Targets	Characteristic Features	References
Cardiac specific								
Cardiac troponin T†	An emerging marker for detecting CAD or ACS in CKD pts.	Troponins are released from cardiac muscle in proportion to the degree of muscle injury.	Plasma ELISA	No	No	Pts with CKD and suspected ACS	In pts with AKD and suspected ACS, cTnT sensitivity (71% to100%) and specificity (31% to 86%),	[51-53]
Cardiac troponin I†	An emerging marker for detecting CAD or ACS in CKD pts.	Troponins are released from cardiac muscle in proportion to the degree of muscle injury.	Plasma ELISA	No	No	Pts with CKD and suspected ACS	In pts with AKD and suspected ACS, cTnI sensitivity (43% to 94%) and specificity (48% to 100%).	[52,53]
High-sensitivity TnT†	An emerging high-sensitivity troponin marker in pts with CKD	Elevated hsTnT in pts with CKD due to previous MI, unrecognized ischemia, cardiac stress, ventricular fibrosis, left ventricular hypertrophy and dilation, inflammation, endothelial dysfunction, and other cardiac injury.	Baseline ≤ 5.0 to 378.7 pg/ml	No	No	Pts with mild to severe CKD	**A sensitive and specific marker** for incident HF in pts with CKD (the highest quintile > 26.5 ng/ml for HF vs. undetectable hsTnT for individuals) (a 5-fold risk of incident HF). Note: higher hsTnT levels in men vs women and in blacks vs. whites.	[54]

Galectin-3[†]	An emerging myocardial fibrosis marker for prognosis of CHF.	Gal-3 is a soluble β-galactoside-binding lectin that plays a role in cardiac fibrosis and remodeling in CHF.	Plasma, ELISA (BG medicine, Inc., USA).) (Cut-off value = 17.7ng/mL)	No	No	Theraprutic potential in pts with chronic HF.	**A good prognostic marker** for mortality of pts with CHF (AUC-ROC = 0.612) (Value levels 20.1±8.1 for the died vs. 17.5 ±7.4 ng/mL for survivors). **A prognostic marker** for mortality of pts with CHD. MRAs treatment does not affect prognostic value of > 17.8ng/mL. **A non-heart target specific** (fibrosis of liver and kidney also involved).	[55,56]
B-type natriuretic peptide	An emerging marker of diagnosis, prognosis, and management of HF pts and CKD pts.	A hormone produced by ventricular myocardium in response to ventricular stretching and wall stress.	Plasma ELISA	No	No	Identifying pts with any degree of cardiac dysfunction; Identifying pts at increased risk for sudden death; Helping clinicians in planning discharge of HF pts; Therapeutic targets: HF in elderly pts, significant different from standard therapy.	**A high sensitivity and accuracy:** Concentration of >100 pg/mL diagnosed HF with a 90% sensitivity and 76% specificity. **A useful marker** of cardiovascular risk in CKD ptsand progression of decreased renal function.	[52,55]
N-terminal pro b-type natriuretic peptide	An emerging marker of diagnosis, prognosis, and management of HF pts and CKD pts.	NT-proBNP is secreted from cardiomyocytes in response to myocardial stretch. It reflects myocardial stress induced by volume or pressure changes. Its levels increase with increasing left ventricular mass.	Baseline ≤5 to 35,000 pg/ml.	No	No	Therapeutic targets, Pts with mild to severe CKD	**A sensitive, specific and predictive marker** for incident HF in pts with CKD (the highest quintile > 433.05 ng/ml for HF vs. < 47.6 ng/ml for lowest quintile of individuals)(a 10-fold higher rate of incident HF). **A useful marker** of cardiovascular risk in CKD pts. **A predictor** of mortality in CKD pts. AUC-ROC =0.795 NT-proBNP**, A prognostic marker** of predicting CHF and acute coronary symptom. Note: Half-life of proBNP is longer and its levels are more stable than BNP and less affected by acute stress.	[52,55,57]
Creatine kinsase myocardial band	An emerging cardiac marker for predictive AKI	CK-MB released from damaged myocardium. Higher levels reduce cardiac reserve at baseline and result in hemodynamic instability, whereby they lead to greater risk of postsurgical AKI.	Beckman Coulter Access II instrument for CK-MB.	No	No	Prediction of postoperative AKI in children with cardiac surgery.	**A good predictive marker** (AUC-ROC for CK-MB = 0.77).	[58]

Heart-type fatty acid binding protein	An emerging cardiac marker for predictive AKI	h-FABP released from damaged myocardium. Higher levels reduce cardiac reserve at baseline and result in hemodynamic instability, whereby they lead to greater risk of postsurgical AKI.	Evidence Investigator Cytokine Custom Array for h-FABP	No	No	Prediction of postoperative AKI in children with cardiac surgery.	**A good predictive marker** (AUC-ROC for h-FABP = 0.78)	[58]
Supressor of tumorigenicity-2	A emerging marker of cardiomyocyte stress, cardiac remodeling and fibrosis	ST2 is an IL-1 receptor family member expressed in cardiac myocytes, fibroblasts and endothelium. In response to inflammation and cardiac stress, IL33/ST2 signaling is activated and soluble ST2 is released into blood. ST2 acts as cardioprotective signaling pathway resulting in reduced hypertrophy and myocardial fibrosis.	ELISA (RandD Systems Europe, Ltd., UK).	No	No	Potential value of ST2 for guidance of therapy with ACEi, ARBs, MRAs, and β-blockers.	**A predictive of cardiovascular admission or WRF** in pts with pharmacologically optimised CHF; **A good biomarker**�II (AUC-ROC =0.778). **A cardiovascular prognostic marker in CHF.** It service as a guideline-endorsed biomarker of cardiovascular risk.	[55,59-62]
Glutamic acid decarboxylase 15	A emerging markers of CHF with CAD	A stress protein of transforming growth factor-β superfamily (also known as macrophage inhibitor cytokine-1). It has protective effect on coronary artery. It involves in myocardial injury and fibrosis.	Plasma (ELISA): USCN Life Science, Inc. China).	No	No	CHF pts.	**A diagnostic markers** of CHF with CAD; **A good biomarker**�II **(AUC-ROC = 0.804).** **A prognostic marker** of predicting CHF and acute coronary symptom.	[57]
Cardiorenal specific								
α-2 microglobulin	An emerging novel marker of PMI and diabetes.	α2M is synthesized in liver and locally by macrophage. α2M acts as a transporter for cytokines/growth factor and an endogenous inhibitor of circulating proteases. Human cardiac isoform of α2M is identical to human serum monomeric α2M.	Serum or plasma (ELISA)	No	Proteomic analysis of serum example.	Diabetic pts	Cardiac isoform of α2M: **A diagnostic marker** of diabetic pts with PMI or cardiac disease; Serum monomeric α2M: **A diagnostic marker** of diabetic nephropathy (positive correlations between α2M with urinary albumin and HbA1c.)	[63,64]
Asymmetric dimethyl arginine	An emerging marker of CKD and cardiovascular event.	An endogenous inhibitor of NOS. ADMA has profound renal hemodynamic effects.	Plasma	No	No	No	**A strong predictor** of renal disease progression in pts with CKD. ADMA is associated with progression of carotid intima media thickness, cardiac remoering, and left ventricular hypertrophy.	[52,65]
Renal specific								
Glomerulus-specific								

Albumin†	An emerging marker of monitoring progression of CKD.	Low concentration of protein in urine in terms of its large size and selectivity of glomerular filtration barrier and tubular reabsorption.	No	Normoalbuminuria, microalbuminuria, macroalbuminute (UACR <30mg/g, 30 to 299 mg/g, > 300 mg/g, respectively).	No	No	**A prognostic marker** for monitoring reduced GER, progression of CKD, mortality risk.	[66]
Cystatin-C†	An emerging marker of kidney filtration capacity.	A protein of cysterine proteinase inhibitory family, which passes glomerular basement membrane and then it is reabsorbed.	Serum	No	No	Pts with CHF.	**A prognostic** marker for more accurate estimating GFR and reflecting a mild or moderate decrease in renal function in pts with CHF; No age, gender, food, and body mass affected.	[66]
Podocin	An emerging marker of glomerular disease.	Podocin (NPHS2) is a component of glomerular slit-diaphragm, with major regulatory functions in renal permeability of proteins. Podocinloss of podocin may influence the outcome of proteinuric renal disease.	No	Urine (ELISA)	Urine podocin/ nephrin ratio mRNA as a podocyte stress biomarker.	A new therapeutic insight for CKD.	**A predictor of progression** of CKD (In pts with lupus nephritis, podocyturia with anti-podocin correlated as well as urinary protein/ creatinine ratio showed significant correlation with degree of lupus disease activity).	[67,68]
Nephrin	An emerging marker of glomerular diseases.	A transmembrane protein that is specifically located at the slit diagphragm of glomerular podocytes. It functions as a renal filtration barrier and regulates excretion.	No	Urine (ELISA)	A defect in gene for nephrin, NPHS1 recognized.	NO	The number of podocytes and levels of nephrin in urine were significantly higher in lupus nephritis, focal segmental glomeronephritis, and pts with severe proteinuria. A positive correlation between urinary nephrin expression and UACR.	[69]
Proximal tubular-specific								
Kidney injury molecule-1†¥	An emerging marker of renal dysfunction and worse outcome in CHF.	A transmembrane glycoprotein expressed in proximal tubular cell. Injury to these tubular cells leads to urinary level increase.	Yes	Yes	No	No	**A prognostic** marker for more accurate estimating GFR and WRS in pts with CHF.	[66]
Kidney injury molecule-1†¥	An emerging blood biomarker for CKD pts.	Release of KIM-1 into the blood is due to loss of polarity of injured tubular cells, increased transepithelial permeability, and altered microvasculr permeability.	Serum	Urine	No	CKD pts.	**A specific and sensitive marker for CKD of various etiologies; A predictor of progressive renal decline:** In a cohort of pts with type I diabetes and proteinuria, serum KIM-1 levels at baseline strongly predicted rate of eGFR loss. and risk of ESRD during 5-15 yrs of follow-up, after adjustment for baseline urinary albumin-to-creatinine ratio, eGFR, and Hb1Ac.	[70]

Trefoil factor 3†	An emerging marker for kidney injury in CKD pts.	TFF3, a small peptide, is expressed in tubular epithelial cells. Injury to tubular cells leads to increase of TFF3 in sera and urine. However, glomerular injury is not associated with urinary TFF3 excretion. TFF3 may play roles in regeneration and restitution, and in kidney damage repair, as well as in EMT process.	Serum (ELISA)	Urine (ELISA)	TFF3 mRNA may be candidate marker.	CHD pts.	**A predictor for progression of kidney injury for stages 1-5** (Correlation of serum TFF3 levels with CKD stage: 23.6ng/ml,29.9 ng/ml, 54.9 ng/ml, 85.0 ng/ml, 176.6 ng/ml for stages 1-5, respectively vs. normal control 17.8ng/ml).	[71]
Neutrophil gelatinase associated lipocalin	An emerging marker of renal dysfunction in CHF.	A lipocalin protein produced by kidney. Injury to proximal tubule leads to urinary level increase. NGAL mRNA is transcribed and overexpressed in loop of Henle and collecting duct, and thus urinary levels increases significantly.	Yes	Urine			**A prognostic** marker for more accurate estimating GFR and WRS in CHF pts. **A weak marker of risk for renal function decline**, but might be a predictor of cardiac event in HF pts with and without renal disease.	[52,66]
N-acetyl-β-D-glucosaminidase	An emerging marker of renal dysfunction and worse outcome in CHF.	A protein produced in proximal tubular cells, tubular injury leads to its excretion into urine.	No	Urine	No	No	**A prognostic** marker for more accurate estimating GFR and WRS in pts with CHF.	[66]
Interleukin-18	An emerging marker of tubular injury CHF.	A cytokine secreted by proximal tubular cells.	No	Yes	No	No	**A prognostic** marker for WRS in pts with CHF. Not high specific;	[66]
L-type fatty acid binding protein	An emerging marker of tubular injury CHF.	A protein binding free fatty acids. Tubular injury leads to excretion of L-FABP.	No	Yes	No	No	**A prognostic** marker for worse outcome in CHF.	[66]
Vascular endothelial cell growth factor	An emerging marker of CKD	An endothelial cell-specific mitogen. The effects of VEGF on endothelial cells includes cell motility and proliferation, upregulation of NOS, production of prostaglandins, modulation of apoptosis, permeability, protection mechanisms to manage increased shear stress, and leukocyte adhesion.	Plasma	No	No	Diabetic CKD pts.	A predictor of progression of ESRD.	[72]
Osteopontin	An emerging marker of incident diabetic nephropathy	A multifunctional protein that is biosynthesized by a variety of tissues including kidney. OPN is expressed in immune cells (neutrophils, T and B cells, and has chemotactic property.	Serum (ELISA)	No	No	Pts with type 1 diabetes.	**A strong predictor of incident diabetic nephropathy, CVD, and all-cause mortality in pts with T₁D** (serum OPN was higher in pts developed microalbumin, progressed to ESRD, incident CVD, or died).	[73]

Megalin	An emerging marker of dysfunction of proximal tubular reabsorption.	A large multi-ligand endocytic receptor that play a role in reabsorption of filtered plasma proteins, hormone and vitamins by proximal tubules.	No	Urine	Megalin-encoding gene (*LPR2*)	Pts with DB/FOAR syndrome	A diagnostic marker for DB/FOAR due to proximal tubular dysfunction of megalin.	[74]
Unknown site-specific								
Uromodulin	An emerging marker of CKD.	Uromodulin (Tamm-Horsfall protein) is the most abundant urinary protein in healthy individuals and play a role in progress of IgA nephropathy.	No	Urine (ELISA)	No	No	A predictor of IgA nephropathy (Low urinary uromodulin levels were associated with a faster eGFR decline, interstitial fibrosis/ tubular atrophy, and gender (higher in female than in man).	[75]
Wilm's tumor-1 protein	An emerging marker of CKD.	A transcription factor in urinary exosomes. The sequence of events leading to formation of exosomes is initiated by fusing of endocytic vesicle with multivesisicular bodies MVB), forming internal vesicles within MVB due to invaginated membrane, fusing of MVB with plasma membrane, and then internal vesicles entering extracellular space as exosomes. It is suggested that a rich source of kidney injury biomarkers are present in urinary exosomes because they contain intracellular proteins.	No	Urine (Western blot).	No	Pts with CKD.	**A useful marker** of early podocyte injury in ESRD pts.	[76]

*For biomarkers from preclinical biomarkers translated into clinical setting, several processes are needed, including bridging preclinical biomarkers to clinical biomarkers, validation of the biomarker, transplantation application of preclinical biomarkers into clinical setting, and clinical qualification. The table includes FDA approved 10 biomarker qualification (cTnI, cTnT, Alb, B2M, Clu, CysC, TUP, TFF3, Kim-1, RPA-1) for nonclinical use. The FDA approved biomarkers are also accepted for clinical observation under certain circumstances. Qualification is a conclusion that these biomarkers are sensitive and specific biomarkers for myocardial or kidney damage. FDA also approved 3 biomarkers (Gal3, TIMP-2/IGFBP7) for clinical setting, by using Galectin-3 Assay™ (BG Medicine) and NephroCheck® test (Astute Medical Inc., USA).

§FDA regulates *in vitro* diagnostic devices (IVD), and the biomarkers used in IVD typically include genomic, proteomic, and metabolomic biomarkers. †Cardiac troponins were reviewed by FDA as qualified biomarkers for nonclinical use on February 23, 2012. Qualification is a conclusion that cTnI and cTnT are sensitive and specific biomarkers for myocardial damage.

† 7 biomarkers were selected from 23 markers for kidney toxicity by FDA and EMA as qualified biomarkers for nonclinical use. Qualification is a conclusion that these biomarkers are sensitive and specific biomarkers for kidney damage.

¥FDA and EMA qualified KIM-1 as a urinary biomarker in clinical studies on case-by case basis.

Biomarker abbreviations

α2M = α-2 macroglobulin; ADMA = asymmetric dimethylarginine; Alb = albumin; BNP = B-type natriuretic peptide; CK-MB = creatine kinase-MB; cTnI = cardiac troponin I; cTnT = cardiac troponin T; CysC = cystatin C; hsTnT = high sensitivity troponn T; Gal3= galectin 3; GDF15 = growth differentiation factor 15; L-FABP = the liver type fatty acid binding protein; h-FABP = heart-type fatty acid binding protein; IL-18 = interleukin 18; Kim-1/KIM-1 = kidney injury molecule-1; NAG = N-acetyl-β-D-gl ucosaminidase; NGAL = neutrophil gelatinase-associated lipocalin; NT-proBNP = N-terminal-pro-B type natriuretic peptide; OPN = osteopontin; ST2 = suppression of tumorigenity 2;TFF3 = trefoil factor 3; VEGE = vascular endothelial growth factor; WT-1= Wilms tumor 1.

Other abbreviations

ACS = acute coronary syndrome; ADHF = acute decompensated heart failure; AH = athlete's heart; AHF = acute heart failure; AKI = acute kidney injury; ATL= controls; ATN= acute tubular necrosis; AUC = area under a ROC curve; CAD = coronary artery disease; CHF = chronic heart failure; CKD = chronic kidney disease; CVD= cardiovascular disease; DB/FOAR = Donnai-Barrow/Facio-Oculo-Acustico-Renal; ELISA = enzyme-linked immunosorbent assay; EMA = European Medicines Agency; EMT = epithelial-to-mesenchymal transition; ESRD = end-stage renal disease; GFR = glomerular filtration rate; HF = heart failure; CRS = cardiorenal syndrome; MRAs = mineralocorticoid receptor antagonists; NO = nitric oxide; NOS= nitric oxide synthase; PMI = post myocardial infarction; pts = Patients; RAS = rennin-angiotensin system; ROC = receiver-operating characteristic; T_1D = type 1 diabetes; UACR = urine albumin/creatinine ratio; WRF = worsening renal function; yr = year

Table 1: Clinical biomarkers* used or proposed for type 2 chronic cardiorenal syndrome or type 4 chronic renocardiac syndrome.

a 30% or 40% loss of function over one to two years would be a valid surrogate for the progression of CKD offers some modest hope that clinical trials could be undertaken that would be feasible using this endpoint [24]. As for the albumin: creatinine ratio or urine: protein ratio in the urine, there is considerable controversy over wether or not this endpoint is a valid surrogate. In general, small reductions in urine albumin in the range of 300 mg/g down to 30 mg/g are probably not indicative of major changes in clinical cardiorenal outcomes. However, in patients with diabetic CKD with heavy proteinuria (> 1 g urine protein per day), a large reduction (30-50%) may be a large enough signal that CKD is stabilizing, therefore influencing the future risk of cardiovascular events such as heart failure and the need for renal replacement therapy or all-cause mortality [34]. Of note, the Study Of Diabetic Nephropathy With Atrasentan (SONAR) trial testing low dose atrasentan (endothelin receptor A antagonist) has a unique design that will also test the validity of urine protein as a surrogate in patients with diabetic nephropathy (eGFR 25 to 75 mL/min/1.73 m^2 and a urine albumin creatinine ratio (UACR) 300-5,000 mg/g [35]. In this trial, all subjects (N=4148) are given atrasentan 0.75 mg p.o. qd initially and then are characterized as "responders" who experience a 30% or more reduction in urine protein. Then both the "responders" and "nonresponders" are randomized to atrasentan or placebo for several years with a composite renal endpoint: doubling of serum creatinine (confirmed by a 30-day serum creatinine) or the onset of end stage renal disease (needing chronic dialysis or renal transplantation or renal death). If only the responders benefit from the study drug for the clinical outcomes, then proteinuria will be validated as a surrogate. However if both the responders and nonresponders either benefit or both fail to benefit over placebo, then the uncertainty around the surrogacy of proteinuria as a treatment target will continue.

Agents to Prevent and Control Hyperkalemia

Patiromer calcium and sodium zirconium cyclosilicate are two new oral potassium binders expected to be approved and in clinical use shortly (Figure 3) [36]. Patiromer calcium is a novel exchange resin formulated as beads that contain sorbitol as an adjunctive cathartic which accounts for 50% of weight (2 g sorbitol for every 4.2 g of patiromer) as well as calcium (1.6 g calcium for every 4.2 g of patiromer). Patiromer is insoluble in typical solvents and passes through the GI tract without degradation and has its principal site of potassium in the colon about 7 hours after ingestion. The Polymeric Potassium Binder, in a Double-blind, Placebo-controlled Study in Patients with Chronic Heart Failure (PEARL-HF) demonstrated that in HF patients with hyperkalemia randomized to patiromer calcium were more successfully treated with spironolactone 50 mg/day (91% vs 74% placebo; P = .019) [37,38].

In the Patiromer for the Treatment of Hyperkalemia (OPAL-HK) study, patients with CKD and eGFR 15-59 mL/min/1.73 m^2 who were on at least one ACEI, ARB, or MRA, and had serum potassium concentrations of 5.1-6.4 mEq/L at two screenings were eligible for the trial. In the first part of the trial, 91 subjects with potassium concentrations 5.1-5.4 mEq/L received open-label patiromer 4.2 g PO bid titrated up to average daily dose of 12.8 g and those (n = 151) with baseline potassium concentrations 5.5-6.4 mEq/L received double the dose (8.4 g PO b.i.d. titrated up to 21.4 g average daily dose) for 4 weeks. The maximum dose of patiromer allowed was 50.4 g/day (12, 4.2 g packets). Patiromer resulted in baseline to week 4 potassium reduction (primary outcome) of −1.01 ± 0.03 mEq/L (P < .001). The median change in the potassium concentration from the start of a randomized withdrawal phase out to 4 weeks was + 0.72 mEq/L in the placebo group and 0 mEq/L in the patiromer group receiving an average daily dose of 21.1 g, demonstrating extended suppression of potassium concentrations in the plasma.

Sodium zirconium cyclosilicate (ZS-9, ZS Pharma, Inc) is another novel agent under development as a treatment for acute and long-term chronic hyperkalemia. Sodium zirconium cyclosilicate is an inorganic cation exchanger engineered to have a highly selective, high-capacity crystalline lattice structure to preferentially entrap monovalent cations (specifically excess potassium ions) over divalent cations (e.g., calcium

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Patiromer Calcium

- Organic polymer
- 2-Propenoic acid, 2-fluoro-, calcium salt (2:1), polymer with diethenylbenzene
- and 1,7-octadiene
- Cross-linked polymer of calcium 2-fluoroprop-2-enoate with diethenylbenzene
- and octa-1,7-diene
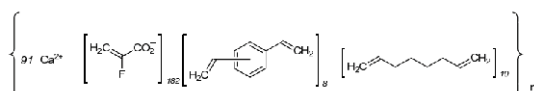
Sodium Zirconium Cyclosilicate (ZS-9)

- Inorganic polymer, selective potassium trap
- Octahedral [ZrO6]2−
Units confers
negative
Charge to the framework, enabling
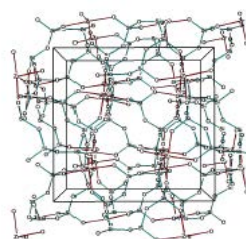Cation exchange

Figure 3: Novel potassium binders approaching approval and use in practice.

and magnesium). Sodium zirconium cyclosilicate also appears to bind ammonium resulting in net acid loss and systemic elevation in plasma bicarbonate. In a double-blind, placebo-controlled clinical trial in patients with hyperkalemia (~66% on at least one ACEI, ARB, or MRA), a total of 753 patients with potassium levels 5.0-6.5 mEq/L, which included patients with CKD, heart failure, diabetes, and those on ACEIs, ARBs, or MRAs, were randomized to receive 1 of 4 doses of sodium zirconium cyclosilicate versus placebo [39]. At 48 hours, there were absolute mean reductions of 0.73 mEq/L in the 10-g group (P<0.0001), as compared with a mean reduction of 0.25 mEq/L in the placebo group. The mean reduction from baseline to 1 hour after the first 10-g dose of sodium zirconium cyclosilicate was 0.11 mEq/L (P = .009) suggesting a potassium binding effect in the upper gastrointestinal tract at the level of the stomach and proximal small intestine. A total of 543/753 patients (72.1%) achieved a normal serum potassium of 3.5-4.9 mEq/L during the initial 48 hour phase, and proceeded to the randomized extended use phase which demonstrated significantly lower potassium levels with zirconium cyclosilicate 5 g and 10 g daily versus the placebo for up to 12 days.

In a second multicenter trial, 258 stable outpatients with a potassium concentration ≥ 5.1 mEq/L (range 5.1 – 7.1 meq/L) at baseline (~67% on at least one ACEI, ARB, or MRA), received 10 g of zirconium cyclosilicate PO t.i.d. during the initial 48-hour open-label phase. Patients achieving normokalemia (3.5-5.0 mEq/L) were randomized to receive sodium zirconium cyclosilicate, 5 g (n = 45 patients), 10 g (n = 51), or 15 g (n = 56), or placebo (n = 85) daily for 28 days [40]. The rates of achieving normokalemia at 24 and 48 hours were 84 and 98%,

respectively. The primary end point was the mean serum potassium levels between placebo and each treatment group (highest to lowest) during days 8 through 29 of the randomized phase which was achieved for all doses of zirconium cyclosilicate versus placebo. The proportion of patients with normokalemia during the randomized phase of the study was significantly higher in all zirconium cyclosilicate groups vs. placebo (80%, 90%, and 94% for the 5 g, 10 g, and 15 g groups, vs. 46% with placebo; P < .001 for each dose vs. placebo). Thus it appears that there will be two new products available in the near future to aide with the management of hyperkalemia in patients with acute and chronic CRS where the use of ACE, ARB, and MRA could be facilitated with better control of serum potassium.

Acute Cardiorenal Syndromes Requiring Hospitalization

Unlike the ambulatory setting, the acute hospitalization of a patient with chronic cardiorenal disease presents considerable risks for acute kidney injury, decompensation of heart failure, need for the intensive care unit, prolonged hospital stay, ESRD, and death. In the schema of five subtypes of CRS, the acute syndromes are Type 1 (cardiac decompensation leading to AKI), Type 3 (AKI leading to HF), and Type 5 (simultaneous cardiac and renal failure in sepsis, etc). In almost all circumstances, the acute CRS involve a complex and multifaceted pathophysiology of acute on chronic heart and kidney disease as shown in Figure 4. Unfortunately, there are no approved therapies that have been shown to reduce or attenuate the degree of acute/injury to both the heart and kidneys. Many acute therapies have been tested in clinical trials, but all have failed to improve outcomes in a convincing fashion,
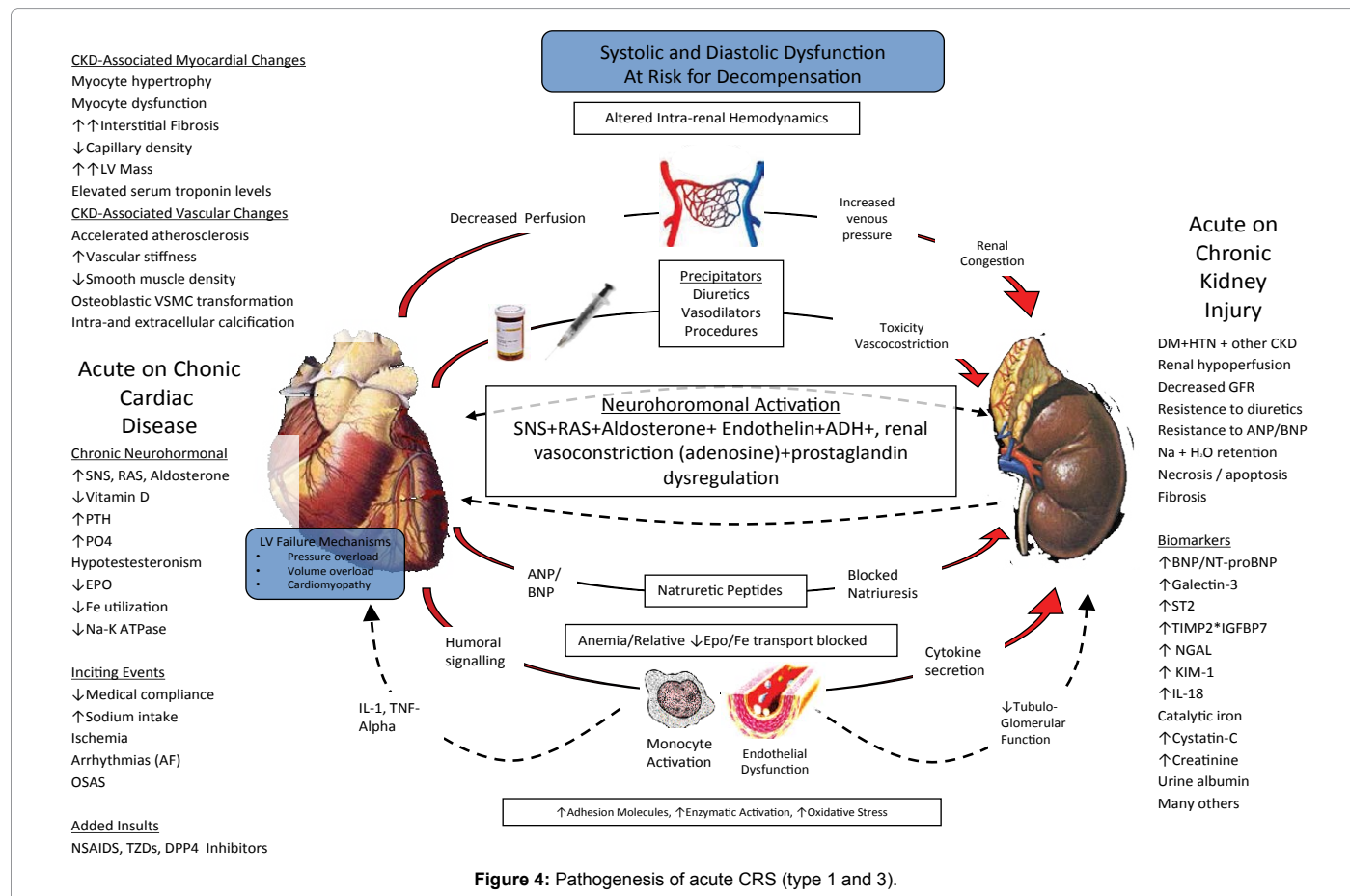

Figure 4: Pathogenesis of acute CRS (type 1 and 3).

including inotropic agents, inodilators, rolophyilline, endothelin receptor antagonists, arginine vasopressin antagonist, and human recombinant BNP. Additionally, among the conventional therapies available to physicians, strategies proven to improve outcomes have been difficult to indentify. Clinical trials have shown that the use of low-dose dopamine, high-dose or continuous infusion of loop diuretics, and ultrafiltration have not broadly benefitted patients at risk or with incipient CRS. The heterogeneity of responses in these studies suggests we have not developed adequate approaches to target those patients that are most likely to benefit (and least likely to be harmed) in our clinical trials [41]. As a result, clinical practice in the hospital setting has not changed much over the past decade with respect to cardiorenal patients. Therefore, we believe that there is a considerable opportunity to develop new vistas in this field to advance the understanding and care for this population. Most of this opportunity will be dependent on phenotypic characterization of the CRS with respect to predominant mechanism (cell signaling, neurohormonal, hemodynamic, electrolyte imbalance) and then a specific therapy applied to the major mechanism. It is unlikely that a "one size fits all" approach to any novel agent in acute development will be broadly successful, including agents such as serelaxin (analogue to the pregnancy hormone relaxin) and omecamtiv mecarbil (myosin activator inotropic agent) [42,43]. A shortcoming of the trials programs for both of these agents is a 48 hour infusion which is simply not long enough to have a meaningful impact on decompensated cardiac or renal function with respect to any of the major mechanisms of acute organ failure. A more realistic approach would be a prolonged infusion (5 or more days) and then conversion to subcutaneous or oral therapy in analogy to the use of antibiotics, corticosteroids, or anticoagulation [44].

Acute Kidney Injury

The definition of acute kidney injury (AKI) was unified by the Kidney Disease Global Outcomes Initiative (KDIGO) in a set of guidelines that incorporated prior AKI definitions by the Acute Kidney Injury Network (AKIN) and the Risk, Injury, Failure, Loss, and End-Stage Kidney Disease (RIFLE) classifications. The KDIGO criteria for AKI (based on the rise in serum creatinine and urine output shown in Figure 5) were helpful to the practice and research community in setting a standard for recognition of acute dysfunction and a baseline definition from which future modifications can be made as have been done for acute myocardial infarction. A list of selected biomarkers for AKI is shown in Table 2. There have been many studies that have shown that independently and together, a rise in serum creatinine (threshold ≥ 0.3 mg/dl) or a reduction in urine output (threshold < 0.5 cc/kg/hr for six hours) is prognostic for the development of more serious renal events such as permanent loss of renal filtration function, ESRD, rehospitalization, and death. However, many of these subtle changes in renal status can be due to transient hemodynamic changes and not damage or death of functional renal parenchymal cells. Thus, the advent of markers of acute tubular injury has represented a major advance in the early detection and confirmation of AKI (Figure 6). Because serum creatinine can take 48 hours to significantly rise, the recognition of AKI based on creatinine is always delayed. While urine output can abruptly decline in AKI, it is commonly manipulated by intravenous fluid administration and use of diuretics. Hence, urine output cannot be a reliable indicator of AKI alone and can be misleading in many cases. However, in the setting of oliguria, it has been shown that a "renal stress test" with a one-time administration of high-dose furosemide can be prognostic for the short-term outcome of ESRD or death [45].

Novel markers that are indicators of tubular cell-cycle arrest (tissue inhibitor of metalloproteinase-2 [TIMP-2], insulin-like growth factor binding protein-7 [IGFBP-7]), protectors against catalytic-iron induced oxidative stress (siderocalin-2 or neutrophil gelatinase associated lipocalin), or promotors of tubular cell recovery (kidney injury molecule-1) have all been shown to be assistive in the diagnosis and prognosis of AKI. In addition, cytosolic enzymes and housekeeping proteins involved in normal cell biologic functions such as alpha and pie-glutathione S-transferase, L-type fatty acid binding protein, and F-isoprostanes can indicate tubular cell injury or death. Increased urinary levels of proteins normally reabsorbed by the proximal tubules can also indicate tubular dysfunction including urinary albumin,
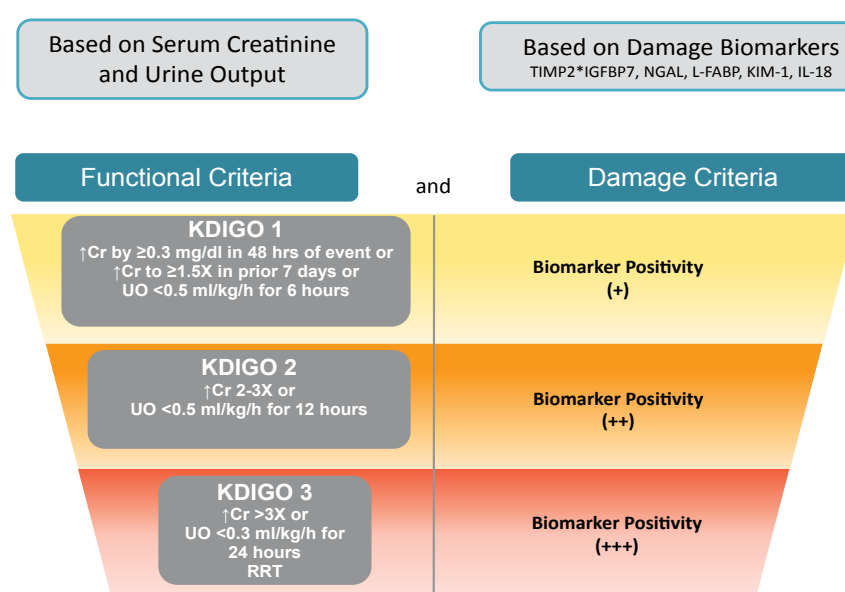

Figure 5: Schema for integrating functional and injury markers for AKI.

Biomarkers	Current Status	Biological and Pathophysiological Properties	Measurable in Plasma, Serum or Blood	Measurable in Urine	In Vitro Diagnostic Target§	Potential Clinical Utility and Guided Therapeutic Targets	Characteristic Features	References
Cardiac specific								
Cardiac troponin I†	FDA approved qualification for nonclinical use.	cTnI is inhibitory component of troponin complex which controls muscle contraction by suppressing interaction between actin and myosin. cTnI is released into the blood due to myocardial injury (necrosis and apoptosis).	Serum cTnI immunoassay	No	Early changes of heart genes in drug-induced cardiotoxicity; Proteomics has higher accuracy than troponins in drug-induced cardiotoxicity.	Diagnostic and monitoring AMI and peri-operative myocardial damage (cardiac transplantation, cardiac by-pass, cardiac dysfunction, congestive heart failure); Possibly for anti-ischemic and cytoprotective therapies by the Ca^{2+}-sensitizer, which targets cTnC. The interaction between cTnI and cTnC mediated by $Ca2^+$ triggers muscle contraction, whereby leading to positive inotropes function. No guided therapeutic targets so far.	**A highly specific** for acute myocardial injury; **A highly sensitive (** limit of detection 3 or < 3 pg/mL); **A predictive, robust, reliable marker**; **Age-relative marker:** Baseline cTnI is higher in normal adult (> 60 years-old) than that in younger (< 60 years-old). Baseline troponins are higher in healthy infants than those in adults; cTnI is not fully within the human myocardium until 9 months of age. **Gender-relative marker** (higher in man than female). Note: Increased troponins may result from non-cardiac conditions, such as **renal damage or septic shock.**	[77-80]
Cardiac Troponin T†	FDA approved its qualification for nonclinical use. FDA cleared as a prognostic aid for all-cause mortality in ESRD	cTnT services to attach the complex to tropomyosin and acts a complex signal amplifier. cTnT is released into the blood due to myocardial injury (necrosis and apoptosis).	Serum cTnT (ELISA)			No guided therapeutic targets so far.	**A highly specific** for acute myocardial injury; **A highly sensitive (** a second –generation cardiospecific assay, Elecys, Roche Diagnostics); **A predictive, robust, reliable marker**.	[77-80]

Galectin-3[†]	FDA cleared as a prognostic aid for HF outcomes (hospitalization and death) reflects interstitial fibrosis that is different from NT-proBNP (loading marker) in response to ventricular stress.	Macrophage-derived Gal-3 induces cardiac fibroblast proliferation and collage deposition in development and process of HF. Secretion of Gal-3 is via a pathway in which cytosolic Gal-3 shifts to plasma membrane and integrates in vesicles extruding from plasma membrane.	Plasma, ELISA (BG medicine, Inc., USA).	No	No	Therapeutic potential. Pts with HF.	**Predicting prognosis** for outcome of HF and preserved LVEF; **A good biomarker[‖]** (AUC-ROC = 0.66-0.67) and for acute HF (AUC-ROC =0.74). Note: baseline levels, Plasma, higher in older and women.	[27,80-82]
B-type natriuretic peptide	Established and FDA cleared as a diagnostic, prognostic, and management aid in patients with suspected and confirmed acute and chronic HF	A hormone secreted by cardiac ventricles in response to excessive stretching of cardiomyocytes. They are released in pts with acute HF.	Plasma: ELISA	No	No	Identifying pts with any degree of cardiac dysfunction; Identifying pts at increased risk for sudden death; Helping clinicians in planning discharge of HF pts; Therapeutic targets: HF in elderly pts, significant different from standard therapy.	**A high sensitivity and accuracy.** Concentration of >100 pg/mL diagnosed HF with a 90% sensitivity and 76% specificity.	[79,80,83]
N-terminal Pro-B-type natriuretic Peptide	An emerging marker of diagnosis, prognosis and prognosis of acute HF.	Secretion due to myocardial stretch and increased wall stress.	Plasma ELISA			Therapeutic targets: HF in elderly pts, statistically significant different from standard therapy.	Cutoff value of 1,078pg/mL for NT-proBNP had greatest prognostic accuracy, however no consistent cutpoint in the literature due to influence of renal clearance.	[79,80,82]
Creatine kinase myocardial band	An older marker of cardiac damage in pts with cardiac surgery	CK-MB released from damaged myocardium. A higher level reduces cardiac reserve at baseline and result in hemodynamic instability, whereby they lead to greater risk of postsurgical AKI.	Beckman Coulter Access II instrument for CK-MB.	No	No	Prediction of postoperative AKI in children with cardiac surgery	**A good biomarker[‖]** (AUC-ROC for CK-MB = 0.77).	[84]
Heart-fatty acid binding protein	An emerging marker of pts with cardiac surgery	h-FABP released from damaged myocardium. A higher level reduces cardiac reserve at baseline and result in hemodynamic instability, whereby they lead to greater risk of postsurgical AKI.	Evidence Investigator Cytokine Custom Array for h-FABP.	No	No	Prediction of postoperative AKI in children with cardiac surgery	**A good biomarker[‖]** (AUC-ROC = 0.78)	[84]
Suppressor of Tumorigenicity-2		Decoy protein for IL-33 receptor family, a potential mediator of myocardial fibrosis.	Soluble form of ST2 for serum measurement plasma ELISA			No guided therapeutic targets so far.		[80]

Cardiorenal specific							
β-2 microglobulin	An emerging marker of CRS.	β2M involving GFR, tissue turnover, and inflammation.	Plasma b2M (ELISA).	No	No	Acute or chronic HF subjects	**β2M services as dual role's marker** for cardiac and renal function and failure. **A sensitive marker of β2M.** Plasma levels of β2M significant higher in CHF pts than in ATL and AH subjects; Strong positive correlation between β2M and TMIP1 in CHF pts and AH subjects versus ATL; Strong positive correlation between β2M with NT-proBNP and GER values in CHF pts; Strong positive correlations between levels of b2M and TIMP1 and severity of cardiorenal remodeling and failure.	[85]
Tissue inhibitor of metalloproteinase -1	An emerging marker of CRS.	TIMP1 inhibiting matrix degradation and over-expressing in substitutive fibrosis	Plasma TIMP1 (Automatic analyzer, AxSym; Abbott)	No	Gene (TIMP1) specific for rat (qPCR).	CHF pts or AH subjects	**A sensitive marker of TIMP1.** Plasma levels of TIMP1 significant higher in CHF pts than in ATL and AH subjects; Strong positive correlation between b2m and TMIP1 in CHF pts and AH subjects versus ATL; Strong positive correlation between b2M with NT-proBNP and GER values in CHF pts; Strong positive correlations between levels of b2M and TIMP1 and severity of cardiorenal remodeling and failure.	[85]

C-type natriuretic peptide	An emerging new diagnostic and prognostic marker	Renal-derived CNP suppresses fibroblast proliferation and collage production; Hypoxia, cytokines, and fibrotic growth factors stimulate its production; Urinary CNP reflects renal structural remodeling prior to kidney disease, and detects in pts with acute compensated HF.	No	Yes	Increased CNP mRNA expression in diabetic rat kidney. **CNP holds promise for diagnostic and therapeutic targets.**	Pts with HF and renal disease states	**CNP service as a double role's marker** for heart failure and renal remodeling (involving tubulointerstitial fibrosis).	[86-88]
Renal specific								
Glomerulus-specific								
Albumin†	FDA approved qualification for nonclinical use.	A most abundant protein in blood plasma that functions as a regulator of colloidal osmotic pressure of blood. Dysfunction of glomerular filtration leads to increased levels of Alb measured in blood and urine	No	Yes	No	No	In pts with cisplatin treatment, urinary excretion of Alb >20mg/L.	[89]
Total urine protein†	FDA approved TUP qualification for preclinical use.	Increased total urinary proteins are due to dysfunction of glomerular filtration and tubular reabsorption.	No	Urine	No	No	Correlation of increased amounts with diabetes or drug-induced nephrotoxicity.	[89]
α1-microglobulin	An emerging marker of AKI.	A protein that is synthesized in liver with half of circulated bound to IgA complex. Its free form is filtered by glomerulus and reabsorbed by proximal tubular cells.	No	Urine (ELISA)	No	Pts with post-cardiac surgery and ATN.	**A sensitive marker** for proximal tubular dysfunction in pts with cardiac surgery. **A prognostic marker of** outcome in pts with nonoliguric acute tubular necrosis. A useful marker of tubular dysfunction in infants at high risk of AKI.	[90]
β-2 microglobulin†	FDA approved qualification for nonclinical use.	A protein present on all nucleated cells. Increased levels of urine B2M indicate dysfunction of glomerular filtration and reabsorption of proximal tubules.	Yes	Yes	Gene specific for rat (qPCR).	No	Increased levels of B2M in pts with idiopathic membrane nephropathy, in pts suffering from with drug-induced kidney damage, and in transplant pts with acute tubulointerstitial rejection.	[89]

Cystatin C[†]	FDA and EMA approved its qualification for preclinical use of drug-induced AKI.	A low molecular weight protein, which is freely filtrated through glomerulus and completely by tubular cells. CysC strongly related to GER.	Yes	Yes	Gene specific for rat (qPCR).	Pts with acute HF or cardiac surgery.	**An early urinary marker** for detecting AKI within 6 hrs after cardiac surgery. **A high sensitive marker to detect type 1 CRS.** **An excellent biomarker**[ǁ] (AUC = 0.92). Serum cutoff values > 0.3mg/dL: specificity of 90% and sensitivity of 77% for AKI ; **Controversy:** Serum CysC is superior to urinary CysC. Serum CysC is not in relation to age, gender, race or muscle mass.	[79,89,91]
Interferon inducible protein-10	An emerging of marker of AKI.	A protein that is secreted by several cell types in response to IFN-γ. It plays roles in chemottraction for immune effector cells and in promotion of T cell adhesion to endothelial cells.	No	Microbead-based sandwich ELISA	In human it is encoded by *CXCL*10 gene.	Pts with AKI.	**A sensitive and specific marker** of AKI (sensitivity of 85% and specificity of 80% in pts with AKI vs. healthy individuals). **A good marker**[ǁ] of AKI (AUC-ROC = 0.89)	[90]
Proximal tubular-specific (also including TUP, α1M, β2M, CysC)								
Kidney injury molecule-1[†¥]	FDA and EMEA approved its qualification for preclinical use of drug-induced AKI	Kim-1is a transmembrane glycoprotein with an immunoglobulin and mucin domain. It is induced in response to ischemia or toxic injury.	No	Urine (ELISA)	No	Pts with acute HF or receiving by-pass surgery or catheterization.	The first injury marker of kidney toxicity qualified by FDA and EMEA. **A highly sensitive marker.** **An excellent biomarker**[ǁ] (AUC-ROC: KIM-1= 0.91-0.99). **A highly specific** for ischemic AKI. An early marker for predicting AKI within 2-24 hrs after post cardiopulmonary bypass.	[79,91,92]

Kidney injury molecule-1[†¥]	An emerging blood marker of AKI	Release of KIM-1 into the blood is due to loss of polarity of injured tubular cells, increased transepithelial permeability, and altered microvasculr permeability.	Plasma or serum	Yes	No	AKI pts.	**A specific and sensitive marker for AKI.** Plasma KIM-1 were higher in AKI pts than in controls or post-cardiac surgery pts without AKI. **An excellent biomarker[‖]** (AUC-ROC =0.98). In pts of cardiopulmonary bypass, plasma KIM-1 increased within 2 days after surgery only in pts with AKI.	[70]
Clusterin[†]	FDA approved qualification for nonclinical use.	Clu as a glycoprotein involved in cell adhesion, membrane remodeling, apoptosis inhibition, phagocyte recruitment. Ischemia, unilateral obstruction or drug insult leads to increased Clu levels.	No	Yes	Gene specific for rat (qPCR).	Increased mRAN expression identified in drug-treated animals.	Immnostaining showed over expressed Clu on human kidney specimens from pts with polycystic kidney disease, acute and chronic renal transplant rejection.	[89]
α-glutathione S-transferase	An emerging marker of AKI.	The tubular enzyme is released from proximal or distal tubular cells and correlated with severity of damaged cells.	No	Urine (ELISA) (Biotrin Ltd, Dublin, Ireland for α-GST).	No	Early intervention can significantly improve the dismal prognosis.	**A good biomarker[‖]** (AUC-ROC of 0.893).	[94]
Neutrophil gelatinase associated lipocalin	An existing marker for acute renal tubular injury.	NGAL is a small 25-kDa protein and belongs to the lipocalin family of proteins. Plasma NGAL is fully filtered through glomerulus and totally reabsorbed in the tubules.	Serum or plasma	Urine (ELISA)	No	Possible as iron chelator because bacteriostasis of NGAL by forming complex with iron-binding siderophores. Pts with acute decompensated HF; Estimating risk of early worning renal function.	**A sensitive marker, but is not a kidney-specific marker (**its synthesis by extrarenal tissues and neutrophils). **An early predictor of subclinical AKI (**within 2h) Elevated plasma NGAL with a cutoff value of 170 ng/mL detecting type 1 CRS within 48-72 h. Serum NGAL ≥ 140 ng/mL had a 7.4 fold higher risk to develop WRF. **Urinary NGAL is not reliable.** Compared with serum NGAL.	[79,91]

N-acetyl-β-D-glucosaminidase	An emerging marker of AKI.	NAG is a lysosomal brush border enzyme in proximal tubular cells. It sheds into urine in response to tubular injury induced by contrast media, toxins, and ischemia.	No	Yes	No	Pts receiving cardiac surgery.	Increased urinary NAG in pts with cardiac surgery to develop postoperative AKI. **A good biomarker[‖]** (AUC-ROC of 0.863).	[79,91,93]
Interleukin-18	An emerging diagnostic marker for AKI.	IL-18 is a proinflammatory cytokine derived from proximal tubular cells. The interaction between inflammasome and other proteins induces an inflammatory response. Urinary IL-18 can be detected after acute proximal tubular damage.	Yes	Urine (ELISA)	No	No	**A sensitive marker.** **An excellent biomarker[‖]** (AUC-ROC = > 90 for ischemic AKI). **An early marker**: increased levels 48 h prior to the increase in serum creatinine. IL-18 is not **kidney-specific marker**.	[79,91,65]
Trefoil factor 3[†]	FDA approved TFF3 qualification for preclinical use.	TFF3 (intestinal trefoil factor) is a protein that is secretory product of mucin producing cells. It plays a role in epithelial restitution. within GI tract and it correlates with downregulation of IL-6 and IL-8 in human intestinal epithelial cells.	No	Urine	No	No	No report of clinical study.	[89]
L-type fatty acid binding protein	An emerging, promising marker.	FABP is located in proximal tubular cells and plays a role in reduction of cellular oxidant stress. Ischemia leads to reduction of L-FABP via proximal tubular reabsorption.	No	Urine (ELISA)	No	Pts receiving cardiac surgery	High sensitivity and specificity to detect AKI in pts with cardiac surgery.	[91]
π- glutathione S-transferase	An emerging marker of AKI.	The tubular enzyme is released from proximal or distal tubular cells and correlated with severity of damaged cells.	No	Urine (ELISA) (Biotrin Ltd, Dublin, Ireland for α-GST).	No	Early intervention can significantly improve the dismal prognosis.	**An excellent biomarker[‖]** (AUC-ROC of 0.929).	[93]
γ glutamyl transpeptidase	An emerging marker of AKI.	The tubular enzyme is released from proximal or distal tubular cells and correlated with severity of damaged cells.	No	Urine (ELISA)	No	Early intervention can significantly improve the dismal prognosis.	**An excellent biomarker‖** (AUC-ROC of 0.95).	[93]
Alkaline phosphatase	An emerging marker of AKI.	The tubular enzyme is released from proximal or distal tubular cells and correlated with severity of damaged cells.	No	Urine (ELISA)	No	Early intervention. can significantly improve the dismal prognosis	**A good biomarker[‖]** (AUC-ROC of 0.863).	[93]

Retinol binding protein	An emerging of marker of AKI.	A protein that is synthesized in liver. It is freely filtrated by glomerulus and reabsorbed by proximal tubule.	No	Urine (ELISA)	No	Pts with AKI and nephrotoxicity.	**A highly sensitive indicator** of proximal tubular dysfunction in pts with AKI. **An early diagnostic marker** of drug-induced nephrotoxicity in pts.	[92]
Fetuin A	An emerging of marker of AKI.	A protein that s synthesized in liver and plays role in regulation of insulin activity, response to inflammation, etc.	No	Urine (immunoblotting)	Exosomal fetuin-A identified by proteomics.	Pts with AKI.	**A diagnostic marker** of AKI (urinary exosomal fetuin-A, EF-A, was much higher in ICU pts with AKI compared with ICU pts without AKI and healthy volunteers).	[92]
Sodium–hydrogen exchanger 3	An emerging of marker of AKI.	The most abundant sodium transporter in renal tubules that is responsible for proximal reabsorption of 60-7-% of filtered sodium and bicarbonate. It is located mainly at apical membrane of proximal tubular cells and loop of Henle.	No	Urine (immunoblotting)	No	Pts with AKI.	**A diagnostic marker** of tubular injury in pts with AKI.	[92]
Cysterin-rich protein-61	An emerging of marker of AKI.	A cysterine-rich, heparin-binding protein and a novel ligand for integrins. It is rapidly induced in proximal straight tubules by ischemia.	No	West blot.	No	No	**A potential marker** of AKI (secretion of urinary Cyr16 within 3-6 hrs after ischemia in rat). No clinical study demonstrating its use.	[92]
Netrin-1	An emerging of marker of AKI.	A laminin-like protein that was secreted in urine within 1 hr following functional injury and rises 30-40 folds in 3 hrs and reaches its peak in 6 hrs after insult. Increase of netrin-1in urine may be due toinduction of protein synthesis and release of pre-synthesis protein.	No	Urine	No	No	**A potential universal marker** of hypoxic injury and nephrotoxicity, but may potentially applicable for various AKI. **A prognostic marker** for renal recovery.	[94]
Hepatocyte Growth Factor	An emerging of marker of AKI.	HGF is secreted by mesenchymal cells and acts as multi-functional cytokines on cells of mainly epithelial cells.	No	Microbead-based sandwich ELISA	No	Pts with AKI.	**A sensitive and specific marker** of AKI (sensitivity of 91% and specificity of 94% in pts with AKI vs. healthy individuals). **An excellent marker**[II] of AKI (AUC-ROC = 0.96)	[92]

Loop of Helen-specific (also including NHE3)								
Distal tubular-specific (also including Clu, NGAL, α-GST)								
CalbidinD28DK	An emerging marker of injury to distal tubule and colleting duct.	A vitamin D-dependent calcium-binding protein of 28D that is found in distal tubules.	Serum	Urine (ELISA)	Gene specific for rat (qPCR).	No	In pts treated with cisplatin, urinary calbidin-D levels were significantly increased 8 days after dosing.	[89,95]
Collecting duct-specific (also including CalbidinD28DK)								
Renal papillary antigen-1[†]	FDA approved RPA-1 qualification for preclinical use.	An uncharacterized antigen that is highly expressed in collecting duct of papillary. It can be detected at high levels following exposure to compounds that induce renal papillary necrosis.	No	Urine (ELISA)	No	No	No report of clinical study.	[89]
Unknown site-specific								
Tissue Inhibitor of Metalloproteinase-2[†]	An emerging marker of AKI	Involving gastrointestinal cell-cycle arrest process; Serving as a marker of cellular stress induced by a variety of insults.	No	A high-sensitivity cutoff value of 0.3 ng/L^2/1000 for predicting non-cardiac surgery patients; 0.5 ng/L^2/1000 for predicting renal recovery after AKI	No	Patients with cardiac surgery or non-cardiac surgery at risk for imminent AKI; Patients predicting renal recovery from AKI.	**A specific marker** for AKI (cutoff value 0.3 ng//L^2/1000 vs. 1.24 for septic, 0.45 for transplant, and 0.47 for post-hepatic surgery) (cutoff value of o.50 vs. 0.81 for cardiac surgery) **A good early marker** (AUC-ROC for AKI = 0.81, 4 hrs after cardiac surgery); **A good high sensitive marker** (AUC-ROC for AKI = 0.85, for AKI stages 2 and 3 = 0.85, for early RRT use = 0.83, for 28-day mortality =0.77);	[96-99]
TIMP-2 x Insulin-like Growth Factor Binding Protein7[†]	An emerging marker of AKI	Involving gastrointestinal cell-cycle arrest process; Serving as a marker of cellular stress induced by a variety of insults.	No	A high-sensitivity cutoff value of 0.3 ng//L^2/1000 for predicting non-cardiac surgery patients; 0.5 ng//L^2/1000 for predicting renal recovery after AKI	No	Patients with cardiac surgery or non-cardiac surgery at risk for imminent AKI; Patients predicting renal recovery from AKI.	**A good reliable marker** (AUC-ROC of TIMP-2 X IGFBP7 for AKI stages 2 or 3 = 0.80).	[96-99]

Interleukin-6	An emerging marker of type 1 CRS	An inflammatory cytokine produced and secreted by superoxide production of hydrogen peroxidase and nitric oxide upregulation. It serves as an oxidative stress marker in type 1 CRS.	Plasma (ELISA) (eBioscience, CA, USA).	No	No	A potential therapeutic target	**A diagnostic marker** of type 1 CRS (IL-6 levels 90.68, 22.19, and 5.9 ng/mL for type 1 CRS, AHF and control, respectively).	[100]
Angiotensinogen	An emerging AKI marker.	It correlates with intrarenal AGT angiotensin II and is an indicator of intrarenal RAS activity	No	Urinary (ELISA, Immuno-Biological Laboratories Co., Ltd., Japan)	No	Predicts AKI in pts with ADHF	**A good specific marker** for AKI (AUC-ROC = 0.84); **A good predictive marker** (AUC-ROC= 0.79)	[101]
Activating Transcription Factor3	An emerging marker of AKI.	A transcription factor in urinary exosomes. The sequence of events leading to formation of exosomes is initiated by fusing of endocytic vesicle with multivesisicular bodies MVB), forming internal vesicles within MVB due to invaginated membrane, fusing of MVB with plasma membrane, and then internal vesicles entering extracellular space as exosomes. It is suggested that a rich source of kidney injury biomarkers are present in urinary exosomes because they contain intracellular proteins.	No	Urine(western blot)	No	Pts with AKI.	**A diagnostic marker** of AKI pts, but in normal subjects or pts with CKD. In ischemic (I/R) and nephrotoxic (cisplatin) AKI rat, excretion of urinary exosomal AFT3 was time dependent.	[76]

* For biomarkers from preclinical biomarkers translated into clinical setting, several processes are needed, including bridging preclinical biomarkers to clinical biomarkers, validation of the biomarker, transplantation application of preclinical biomarkers into clinical setting, and clinical qualification. The table includes FDA approved 10 biomarker qualification (cTnI, cTnT, Alb, B2M, Clu, CysC, TUP, TFF3, Kim-1, RPA-1) for nonclinical use. The FDA approved biomarkers are also accepted for clinical observation under certain circumstances. Qualification is a conclusion that these biomarkers are sensitive and specific biomarkers for myocardial or kidney damage. FDA also approved 3 biomarkers (Gal3, TIMP-2*IGFBP7) for clinical setting, by using Galectin-3 Assay™ (BG Medicine) and NephroCheck® test (Astute Medical Inc., USA).

§FDA regulates *in vitro* diagnostic devices (IVD), and the biomarkers used in IVD typically include genomic, proteomic, and metabolomic biomarkers.

† FDA approved as qualified biomarkers for nonclinical use.

¥ FDA and EMA qualified KIM-1 as a urinary biomarker in clinical studies on case-by case basis.

∥ AUC-ROC of 0.5 represents no better than expected by random change, AUC-ROC of 0.75, a good biomarker, and AUC-ROC of 0.9, an excellent biomarker.

Biomarker abbreviations

Alb = albumin; AP = alkaline phosphatase; ATF3= activating transcription factor3; BNP = Brain natriuretic peptide; CK-MB = creatine kinase-MB; Clu = clusterin; CNP = C-type natriuretic peptide; cTnI = cardiac troponin I; cTnT = cardiac troponin T; Cyr61 = cysterin-rich protein; CysC = cystatin C; h-FABP = heart-type fatty acid binding protein; HGF = hepatocyte growth factor; IGFBP7 = insulin-like growth factor-binding protein 7; IL-6 = interleukin 6; IL-18 = interleukin 18; Gal-3 = galectin-3; Kim-1 = kidney injury molecule-1 (in preclinical study); KIM-1 = kidney injury molecule-1 (in human study); L-FABP = the liver type fatty acid binding protein; NAG = N-acetyl-β-D-glucosaminidase; NGAL = neutrophil gelatinase-associated lipocalin; NAG = N-acetyl-beta-D-glucosaminidase; NHE3 = sodium/hydrogen exchanger isoform;NT-proBNP = NT-pro-B type natriuretic peptide; RBP = retinol binding protein; RPA-1= renal papillary antigen-1;TFF3 = trefoil factor 3; TIMP-2 = tissue inhibitor of metalloproteinase 2; TUP = total urinary proteins; uAGT = urinary angiotensinogen; α-GST = alpha-glutathione S-transferase; b2M = β2-Microglubin; γGT = gamma glutamyl transpeptidase; π-GST = π-glutathione S-transferase.

Other abbreviations

AKI = acute kidney injury; ADHF = acute decompensated heart failure; AH = athlete's heart; AHF = acute heart failure; AKI = acute kidney injury; ATL= controls; AUC = area under a ROC curve; CHF = chronic heart failure; CRS = cardiorenal syndrome; ELISA = enzyme-linked immunosorbent assay; EMA = European Medicines Agency; GI = gastrointestinal; GFR = glomerular filtration rate; HF = heart failure; HR = hazard ratio; LVEF = left ventricular ejection fraction; pts = Patients; RAS = rennin-angiotensin system; ROC = receiver-operating characteristic; WRF = worsening renal function; yr = year.

Table 2: Clinical biomarkers* used or proposed for Type 1 acute cardiorenal syndrome or type 3 acute renocardiac syndrome.
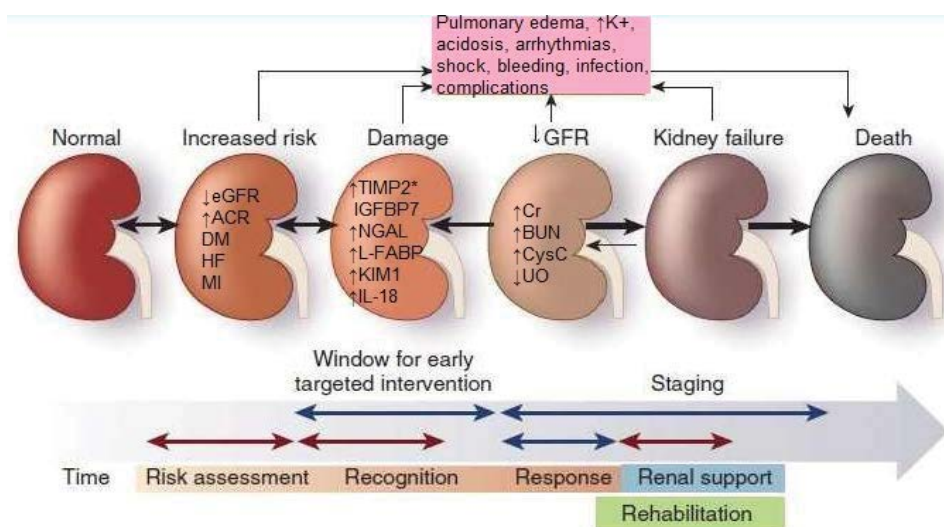
Figure 6: Continuum of kidney function in the setting of CRS.

cystatin-C, and urinary N-acetyl-beta-D-glucosaminidase (NAG). These markers are ideally measured in the urine where they are heavily concentrated. Proteins that are constitutively upregulated in response to chronic kidney disease are less helpful (NGAL, KIM-1) clinically as the baseline value has to be considered in the interpretation of the acute value, and thus one must have multiple measurements at time points [46]. The development of commercial grade assays with the precision and reliability has been a challenge which has been recently overcome with the September, 2014 approval by the U.S. Food and Drug Administration of the NephroCheck® test (Astute Medical, San Diego, CA). This test is a mathematical product of TIMP2 and IGFBP7 expressed in a unit less number with a range of 0.00 to 10.0 and a cutpoint of 0.3 as listed in the package insert. In patients admitted to the intensive care unit, a NephroCheck of < 0.3 had a >90% negative predictive value for the development of moderate or greater AKI [47]. The grey zone for this test appears to be 0.3 to 1.2 where there is uncertainty and likely repeat test will be needed later in time. NephroCheck® values of >2.0 had a high positive predictive value for moderate or severe AKI and may be a future trigger for clinical actions including switching away from nephrotoxic agents (aminoglycosides, vancomycin, non-steroidal anti-inflammatory agents, etc) as well as reducing intravenous fluid administration to avoid impending volume overload that will come with reductions in urine output [48]. A novel biomarker for chronic diabetic nephropathy is urine angiotensinogen, which appears to be 5-6 fold elevated in this condition compared to controls, and appears to risk stratify for the progression of CKD in this population [49].

Thus, novel diagnostic markers will rapidly take a support position in addition to serum creatinine and urine output to: 1) rule out AKI in the setting of pre-renal azotemia, 2) confirm AKI when serum creatinine and urine output are subjective, and 3) serve as a harbinger for moderate or severe AKI to develop over the following 12 to 48 hours in the intensive care unit [50]. Importantly, biomarkers for Type 5 CRS, while probably not helpful in recognizing the clinical condition, may be a critical step forward in the identification of cell, tissue, or organ-specific protective strategies against overwhelming injury. Table 3 gives select biomarkers under investigation for Type 5 CRS. A future hopeful vista for cardiorenal disease is the idea that early detection can lead to strategies that prevent or attenuate renal injury/dysfunction or enhance renal recovery and lead to improved outcomes (Figure 7).

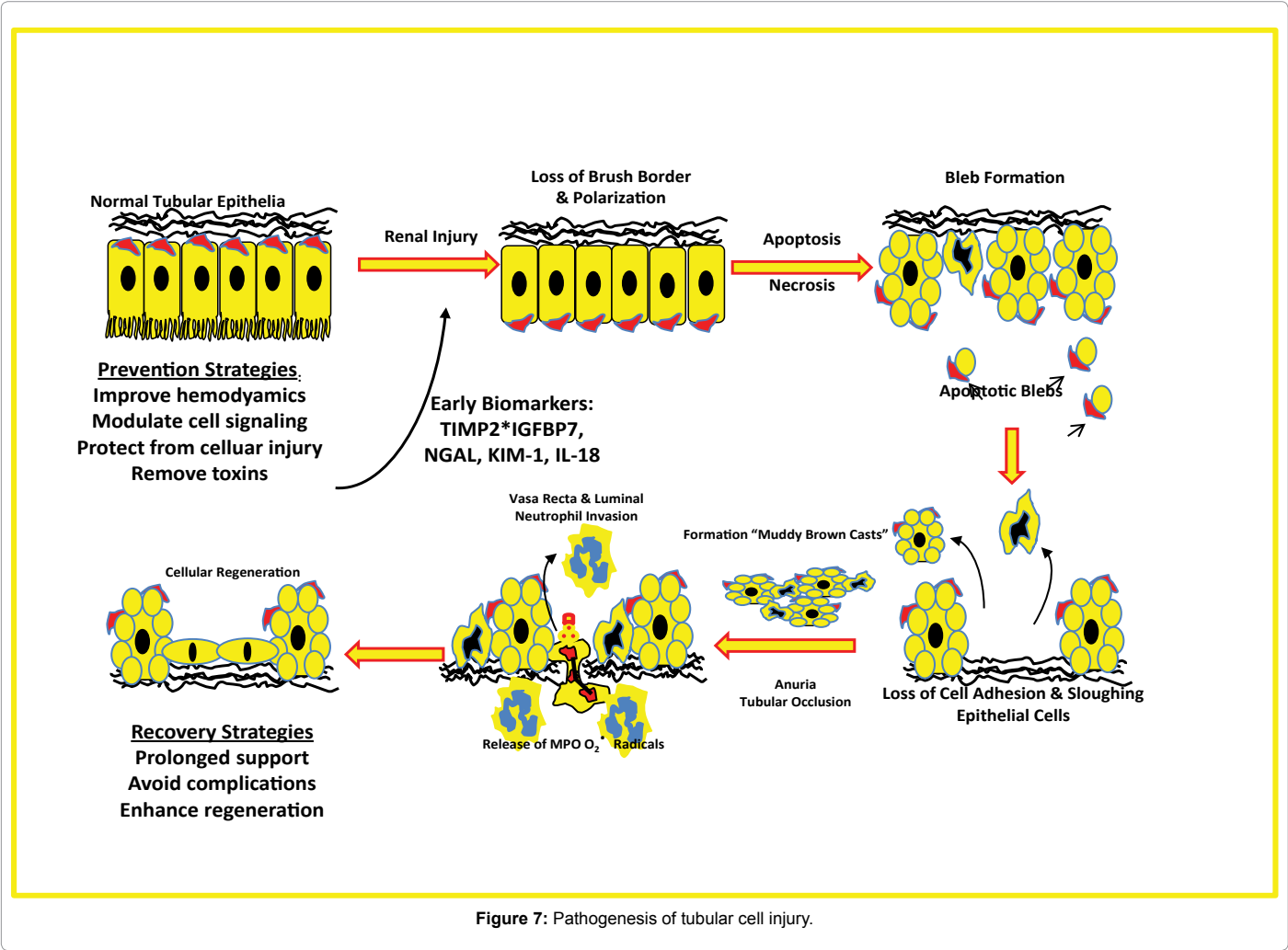## Future Trials and the Need for Continuous Measures of Disease Progression

Acute and chronic CRS do not have specific groups of symptoms that can be used to evaluate benefit of therapies; hence, we have been left to conduct clinical trials with binary endpoints such as the doubling of serum creatinine, ESRD, hospitalization, and death as outcomes. These trials are large, have to be broadly inclusive, and in general have failed to allow the clinical development of products in the hospital and clinic setting. They have been fraught with problems including competing risks (e.g. death before the opportunity to demonstrate and organ effect) and lack of control of concurrent therapies (Figure 8). In addition, the renal functional reserve, or the ability of the kidney to adapt to a decreased mass of functioning nephrons and still carry out filtration sufficiently to keep the plasma pool of creatinine in a reasonable range, makes the assessment of CKD difficult. Renal functional reserve often dictates weather AKI will become clinically recognized in the setting of an acute renal stress such as AHF or sepsis. Hence there has been little opportunity for benefit and considerable opportunity for off-target harmful effects (Figure 8). There has been approximately 10 years with no new disease modifying agents to offer patients with CRS. Thus, despite the concern over the legitimacy of surrogate outcomes, reliable continuous clinical measures are needed that precede hard clinical outcomes in order for the field to progress. Other specialities have witnessed progress with such surrogates as human immunodeficiciency viral load, hepatitis viral load, hemoglobin A1 C, low-density lipoprotein cholesterol, and stages of disease progression in malignancies. So the pursuit of trusted biomarkers and other integrated measures of disease progression are crucial to the future of cardiorenal medicine. In addition, subgroup analyses, as well as more sophisticated approaches to identify heterogeneity of treatment benefit (and harm) should be pursued, and tested in confirmatory trials. These efforts should reduce the time course of development and implementation of beneficial therapies. Continued efforts on safety observations and registries can aide in assuring freedom from unexpected events over prolonged use as well as in the calculus in risk benefit tradeoffs.

Biomarkers	Current Status	Biological and Physiological Properties	Measurable in Plasma, Serum or Blood	Measurable in Urine	In Vitro Diagnostic Target§	Potential Clinical Utility and Guided Therapeutic Targets	Characteristic Features	References
Cardiorenal specific								
B-type natriuretic peptide, albumin	New combined markers for type 5 CRS.	Central (aortic) hemodynamic as a key factor relating to end-organ damage. It can be demonstrated by close relationship between BNP and microalbuminuria, eGFR, aortic pressure, and pulse wave velocity.	Plasma BNP immunoassay (Architect; Abbott and Lumipulse Presto, Tokyo, Japan).	No	No	Potential therapeutic target via controlling central hemodynamic.	**A diagnostic marker** of simultaneous cardiac and renal damage/ dysfunction in pts with hypertension (positive correlation of BNP with UACR, aortic pulse pressure and negative correlation of BNP with eGFR).	[102]
Multibiomarkesr	A proposed panel marker of type 5 CRS	Literature-reviewed proposal	It is dependent on what marker used.	It is dependent on marker used.	No	Potential therapeutic intervention.	Using severe sepsis and septic shock as a model of type 5 CRS, it is suggested that several panels of biomarkers could serve as markers of simultaneous AKI and acute cardiac dysfunction, such as cytokine/chemokines (IL-6, IL-8, TNF etc.), inflammatory cell surface markers , endothelia stress response marker, and acute phase reactants, etc.	[103]
Multibiomarkesr	Novel panel markers of septic acute kidney injury.	A multibiomarker-based model to estimate risk of septic acute kidney injury in pts with septic shock.	Serum protein septic biomarkers	No	No	Potential therapeutic intervention.	In pts with septic shock, sera obtained within24 hrs and 3 days after septic shock. **An excellent markers**: The decision tree (AUC-ROC = 0.95 or 0.83) indicates that the tree was superior to day 1 septic acute kidney injury status alone for estimating day 3 septic acute kidney injury risk. Note: Decision tree is acute kidney injury network scheme.	[104]
Presepsin (sCD14-ST)	Candidate surrogate marker of type 5 CRS	Sepsis is a systemic inflammatory response syndrome. It usually evolves multiple organ dysfunction and failure. sCD14-ST is released into the circulation during monocyte activation upon recognition of LPS from infectious agents.	Plasma (chemilu-minescent enzyme immunoassay, PATHFAST prespsin, Mitsubishi Chemical).	No	NO	Potential guiding therapy for pts with sepsis.	**A candidate surrogate prognostic marker** for mortality prediction in pts with severe sepsis or septic shock (AUC -ROC= 0.69, 0.70, and 0.74 on day 1, 2, and 7, respectively, for prognostic accuracy).	[105,106]

Syndecan-1, thrombomodulin, protein C and FF	Candidate surrogate marker of type 5 CRS	Coagulopathy, microcirculatory failure, and endothelial damage/activation are often present in pts with severe sepsis. Endothelial damage is intimately linked to coagulopathy in severe sepsis and septic shock. Plasma endothelial markers (Syndecan-1, thrombomodulin, protein C) are available for pts with sepsis.	Plasma (ELISA)	No	No	Clinically, endothelial protective interventions would be expected to attenuate sepsis-induced hypocoagulability.	**A panel diagnostic marker** for coagulation and fibriolysis in pts with severe sepsis. Plasma levels of Syndecan-1, thrombomodulin, protein C) were independently associated whole blood hypocoagulability, but fibrinolysis (FF) was inversely associated with syndecan-1 quarties.	[107]

† This table is not intended to be exhaustive.

*For biomarkers from preclinical biomarkers translated into clinical setting, several processes are needed, including bridging preclinical biomarkers to clinical biomarkers, validation of the biomarker, transplantation application of preclinical biomarkers into clinical setting, and clinical qualification.

Biomarker abbreviations

Alb = albumin; BNP = B-type natriuretic peptide; FF = functional fibrinogen; IL-6= interleukin 6; IL-8 = interleukin 8; sCD14-ST= soluble CD14 subtype (presepsin); TNF= tumor necrosis factor.

Other abbreviations

AUC = area under a ROC curve; CAD = coronary artery disease; CRS = cardiorenal syndrome; ELISA = enzyme-linked immunosorbent assay; eGFR = estimated glomerular filtration rate; CRS = cardiorenal syndrome; LBP = lipopolysacchride binding protein; LPS = lipopolysaccharide; pts = Patients; ROC = receiver-operating characteristic; UACR = urine albumin/creatinine ratio.

Table 3†: Clinical biomarkers* used or proposed for type 5 cardiorenal syndrome.

Figure 7: Pathogenesis of tubular cell injury.

Figure 8: Change in priorities needed in future studies to help advance CRS.

Summary

In the past 20 years, we have witnessed progress in common understanding and agreement in the concepts and definitions of acute myocardial infarction, heart failure, CKD, and CRS. A unform lexicon has aided patients, clinicians, and researchers as they deal with the issues of acute and chronic heart and kidney disease. The future is bright in terms of diagnostic and therapeutic strategies that will lead to prolonged quantity and quality of life for patients with these common conditions.

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