Cardiorenal Syndrome in Critical Care: The Acute Cardiorenal and Renocardiac Syndromes

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Heart and kidney disease often coexist in the same patient, and observational studies have shown that cardiac disease can directly contribute to worsening kidney function and vice versa. Cardiorenal syndrome (CRS) is defined as a complex pathophysiological disorder of the heart and the kidneys in which acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ. This has been recently classified into five subtypes on the basis of the primary organ dysfunction (heart or kidney) and on whether the organ dysfunction is acute or chronic. Of particular interest to the critical care specialist are CRS type 1 (acute cardiorenal syndrome) and type 3 (acute renocardiac syndrome). CRS type 1 is characterized by an acute deterioration in cardiac function that leads to acute kidney injury (AKI); in CRS type 3, AKI leads to acute cardiac injury and/or dysfunction, such as cardiac ischemic syndromes, congestive heart failure, or arrhythmia. Both subtypes are encountered in high-acuity medical units; in particular, CRS type 1 is commonly seen in the coronary care unit and cardiothoracic intensive care unit. This paper will provide a concise review of the epidemiology, pathophysiology, prevention strategies, and selected kidney management aspects for these two acute CRS subtypes.

Key Words: Acute coronary syndrome, Acute kidney injury, Cardiac surgery, Cardiorenal syndrome, Heart failure

Consensus Definition and Classification of the Cardiorenal Syndromes

Various organ systems within the human body are intimately connected to each other. This so-called "organ crosstalk" refers to the complex biological communication and feedback between organ systems mediated via various soluble and cellular mediators. In the normal state, this crosstalk helps to maintain homeostasis and optimal functioning of the human body. However, during disease states this very crosstalk can carry over the influence of the diseased organ to initiate and perpetuate structural and functional dysfunction in other organs.[1,2]

Heart and kidney disease often coexist in the same patient in acute and chronic states. Observational and clinical trial data have accrued to show that acute/chronic cardiac disease can directly contribute to acute/chronic worsening kidney function and vice versa. Considering the complex and bidirectional relationship between these two organs, the Acute Dialysis Quality Initiative recently proposed a consensus definition and classification of cardiorenal syndromes (CRS).[3] CRS is defined as "a complex pathophysiological disorder of the heart and the kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ." The classification into five subtypes is based on the primary organ dysfunction, whether heart (called "cardiorenal" syndromes) or kidney (called "renocardiac" syndromes), and on whether the organ dysfunction is acute or chronic (Table 1).[3] The classification is not intended to be static; it is acknowledged that many patients may transition between different CRS subtypes during the course of their disease.[4] An example of such a situation is that of a patient with chronic heart failure (CHF) and CKD; that patient is considered to have CRS type 2. Many such patients may have an episode of acute decompensation requiring hospitalization that may be complicated by acute kidney injury (AKI) in 24-45% of cases; the patient will then slip into CRS type 1. Treatment of the acute decompensation will restore the patient to their baseline state. The AKI in such situation is often transient, and the kidney function recovers to its preexisting level; the patient then moves back into CRS type 2. Further subclassifications into transient or reversible dysfunction and slowly or acutely progressive vs stable disease are avoided to keep the classification parsimonious.

Acute Cardiorenal and Renocardiac Syndromes

Epidemiology

Of particular interest to the critical care specialist are CRS type 1 (acute cardiorenal syndrome) and type 3 (acute renocardiac syndrome). Both subtypes are encountered in high-acuity medical units; in particular, CRS type 1 is commonly seen in the coronary care unit and cardiothoracic intensive care unit (ICU).

CRS Type 1

CRS type 1 is characterized by an acute deterioration in cardiac function that then leads to AKI (Table 1). The spectrum of acute cardiac dysfunction that could result in AKI includes acute decompensated heart failure (AHF), acute coronary syndrome (ACS), and postcardiotomy low cardiac output syndrome, among others. There

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are several studies describing the epidemiology of CRS type 1, most commonly referred to in the literature as "worsening renal function" in AHF and ACS. An extensive review on this topic can be found elsewhere.[4,5] Increases in serum creatinine (sCr) ranging from 0.1 to 0.5 mg/dL and 25-50% from baseline have been used to define CRS type 1. Other definitions used in the literature include change (Δ) in estimated glomerular filtration rate (eGFR; eg, decrease in eGFR by 25%), by either ΔsCr and/or urine output (eg, <20 mL/hour), or by Δblood urea nitrogen (eg, increase by 50%). Different studies also considered variable timeframes for ascertainment of this end point, which would also influence epidemiologic estimates. Most commonly, the period of observation is within the hospital admission, but other studies have also looked at 2 weeks[6] or at a longer term such as 6 months.[7] It has been recommended that established AKI consensus definitions/classifications (RIFLE, AKIN, KDIGO)[8-10] and a defined relevant time frame (eg, first 7 days of hospitalization) be used in future studies enrolling AHF/ACS patients.[4] This would enable integration of type 1 CRS into the broader context of AKI and permit greater standardization of data across future epidemiologic investigations.

Recognizing the limitations of having varied definitions, CRS type 1 has been described in 27-45% of hospitalized AHF patients[11-17] and in 9-54% of ACS patients[6,18–23] (Fig 1). A significant proportion of cases occurs in the first 3-5 days after admission in AHF and ACS.[13,18,24] It is likely that the pathophysiology of CRS type 1 (discussed further below) may vary at different time points. For example, early AKI may be related to a low cardiac output state and/or marked increase in venous pressure. On the other hand, investigations (ie, cardiac catheterization and contrast media exposure) or interventions (ie, furosemide, angiotensin-converting enzyme [ACE] inhibitors) may be the factors responsible for CRS type 1 occurring later in the hospital course.

Several risk factors have been identified in the literature. Nonmodifiable risk factors include a history of diabetes or prior admissions for AHF or myocardial infarction and evidence of more severe cardiac dysfunction at the time of presentation (eg, presence of pulmonary edema or tachyarrhythmias, worse Killip class,[25] or lower ejection fraction[6,15,18]). Worse kidney function on admission, whether defined by sCr or eGFR, has consistently been associated with higher risk for CRS type 1 in almost all studies. In terms of the so-called modifiable risk factors, high-dose diuretic (eg, daily furosemide dose >100 mg/day or in-hospital use of thiazides) and/or vasodilator therapy as well as higher radiocontrast volumes (eg, contrast media volume-to-creatinine clearance ratio [V/CrCl] >3.7) during cardiac catheterization and intervention have been frequently cited in epidemiologic studies.[11,12,15,17,24,26,27] However, it is likely that these are merely surrogate markers for more severe acute cardiac dysfunction or ischemia.

In AHF and ACS, the development of CRS type 1 has been associated with worse clinical outcomes, rehospitalization, and increased health care expenditures.[16,17,19,28] The mortality risk associated with CRS type 1 is most pronounced early on, but it persists beyond the short term.[28] Indeed, an increased risk for death can be seen as far as 10 years out from the index hospitalization for acute myocardial infarction (AMI).[21] Furthermore, a biological gradient has been observed between severity of CRS type 1 and mortality risk.[21,28] More recently, CRS type 1 has also been associated with an independent higher risk for ESRD; likewise, the more severe the AKI episode, the higher the risk of ESRD.[20]

CLINICAL SUMMARY

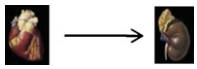
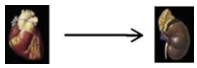
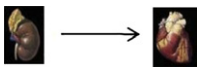
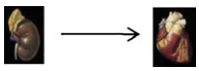
- Cardiorenal Syndrome (CRS) is a complex pathophysiological disorder of the heart and the kidneys wherein acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ.
- CRS Type 1 (acute cardiorenal syndrome) is characterized by an acute deterioration in cardiac function, which leads to acute kidney injury (AKI).
- In CRS Type 3 (acute renocardiac syndrome), AKI leads to acute cardiac injury and/or dysfunction, such as cardiac ischemic syndromes, congestive heart failure, or arrhythmia.
- The management of these acute CRS subtypes is challenging due to the multitude and complexity of pathophysiological interactions between heart and kidney.

CRS Type 3

CRS type 3 is characterized by AKI that then leads to an acute cardiac injury and/or dysfunction, such as AMI, congestive heart failure (HF), or arrhythmia (Table 1). Acute kidney conditions that are typical for this syndrome include cardiac surgery-associated AKI, AKI after major noncardiac surgery, contrast-induced AKI (CI-AKI), other drug-induced nephropathies, acute glomerulonephritis, and rhabdomyolysis.

In contrast to CRS type 1, there is a relative paucity of data regarding the epidemiology of CRS type 3. Perhaps the earliest clinical reports of CRS type 3 were that of electrocardiographic (ECG) changes in patients with AKI and electrolyte disorders dating back to 1961.[29,30] In 60 patients with kidney failure, increased PQ interval was noted among the patients with K greater than 7 meq/L, and a prolonged QT wave was associated with the presence of hypocalemia.[29] The authors noted that ECG changes were more frequently observed among AKI patients as compared with those with CKD, even at similar levels of potassium. In another early series of 69 AKI patients, ECG was performed before and after

Table 1. Classification of CRS

Class	Type	Description	Clinical Scenarios (Examples)
1	Acute CRS 	Abrupt worsening of cardiac function leading to AKI	- AHF - Cardiac surgery - ACS - CIN after coronary angiogram
2	Chronic CRS 	Chronic abnormalities of cardiac function leading to CKD	- IHD/hypertension - CHD - CHF
3	Acute renocardiac syndrome 	Abrupt worsening of renal function leading to acute cardiac dysfunction	- Acute pulmonary edema in AKI - Arrhythmia - CIN with adverse cardiac outcomes
4	Chronic renocardiac syndrome 	CKD leading to chronic cardiac dysfunction	- Cardiac hypertrophy in CKD - Adverse cardiovascular events in CKD - ADPKD with cardiac manifestations
5	Secondary CRS 	Systemic disorders causing cardiac and renal dysfunction	- Sepsis - SLE - DM

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; CHD, congenital heart disease; CIN, contrast-induced nephropathy; DM, diabetes mellitus; IHD, ischemic heart disease; SLE, systemic lupus erythematosis.

hemodialysis.[30] They were divided into 4 groups based on predialysis potassium level (<3.8, 3.8-5.1, 5.1-6.5, and >6.5 meq/L). All patients exhibited tachycardia with shortening of PQ and QRS intervals after hemodialysis. This shortening was most marked among the patients with significant hyperkalemia (>6.5 meq/L) before dialysis. In contrast, U wave was observed in all hypokalemic AKI patients before dialysis and disappeared only in some patients afterward.

Very few clinical studies that focused on AKI have reported on the event rates of acute cardiac dysfunction. Therefore, estimates of incidence and associated

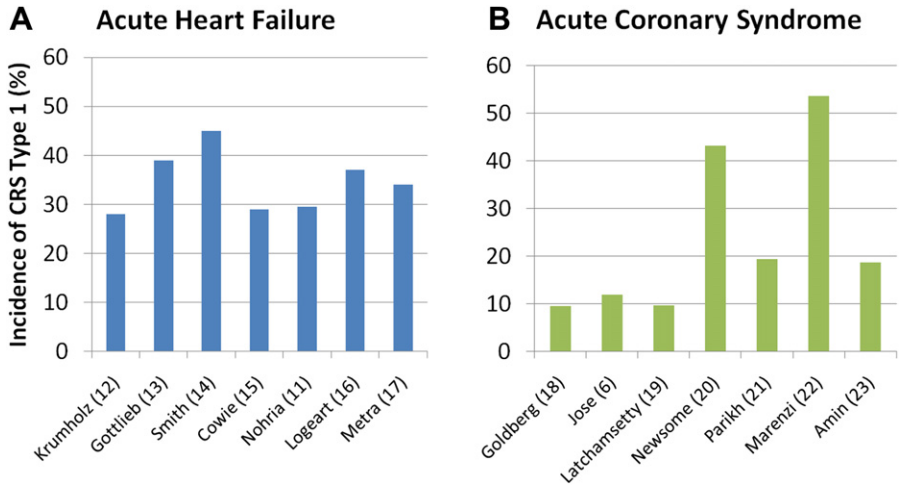


Figure 1. Incidence of CRS type 1 in selected studies on (A) AHF and (B) ACS.

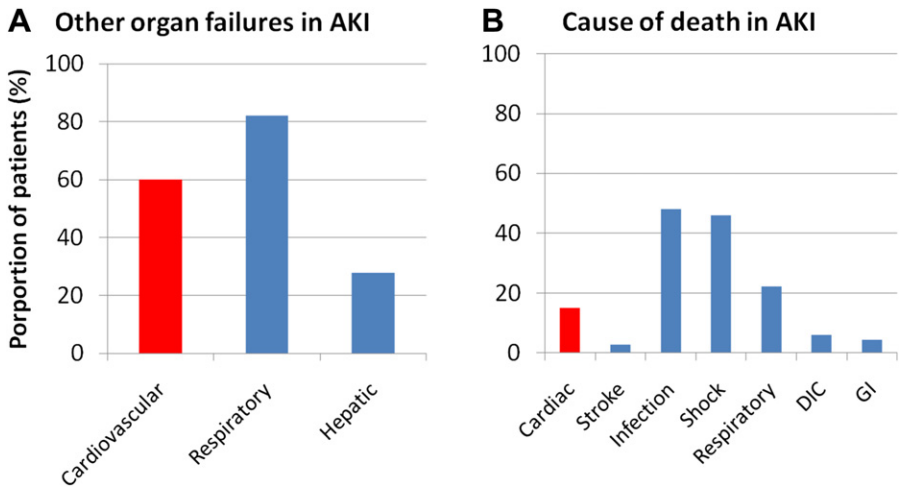


Figure 2. Other organ failures seen in AKI patients (A); adapted with permission from Liano et al.[31] Reported causes of death in AKI patients (B).[31–32]

outcomes of CRS type 3 are challenging. In a multicenter AKI cohort, the organ failures most commonly seen were respiratory, cardiovascular, and hepatic failure[31] (Fig 2A). The mortality of AKI patients in the ICU increased concomitantly with the number of other organ failures. These same authors reported the cause of death in 748 cases of AKI in 13 hospitals in Madrid over a 9-month period.[32] Heart disease was the reported cause of death in 15% of AKI patients; the top causes were infection, shock, and respiratory disease (Fig 2B). With the lack of good quality data on this syndrome, it has been recommended to include cardiovascular events as outcomes in studies focused on AKI, to conduct primary investigations to characterize factors associated with susceptibility for acute cardiac dysfunction in AKI, and to determine whether these factors may be preventable and/or modifiable.[4]

Pathophysiology

CRS Type 1

The presence of AHF may affect kidney function by several mechanisms including disturbed hemodynamics, presence of external factors, and immune-mediated processes.[33,34]

At the onset of AHF, particularly with the presence of systolic dysfunction and decreased cardiac output, kidney arterial underfilling and increased venous congestion are expected complications leading to decreased glomerular filtration rate.[35]

A lower kidney perfusion in the setting of AHF overactivates the renin-angiotensin-aldosterone system (RAAS), promoting water and sodium retention, which will contribute to systemic and kidney hypertension and consequently endothelial and glomerular injury. Additionally, angiotensin II and aldosterone have profibrotic and proinflammatory properties that further contribute to kidney damage.

Some drugs commonly prescribed for the treatment of AHF can also contribute to development of AKI by disturbing systemic and kidney hemodynamics. Diuretics are recommended in AHF to control dyspnea and edema, but their use may be complicated by excessive intravascular volume depletion and further compromise kidney perfusion.[36,37] Diuretic resistance may also complicate the clinical picture of CRS type 1 by acutely or chronically increasing sodium retention.[38] ACE inhibitors, angiotensin receptor blockers (ARBs), and aldosterone receptor antagonists are included in the protocols for the management of HF[39] because these drugs have been shown to significantly improve the survival of these patients in many randomized control trials.[40-46] However, they affect kidney hemodynamics, and their use must be carefully monitored to avoid AKI in decompensated patients.

Another important iatrogenic nephrotoxin in AHF and ACS is radiocontrast media for imaging procedures. Iodinated contrast agents induce intense and prolonged vasoconstriction at the corticomedullary junction of the kidney and directly impair the autoregulatory capacity of the kidney through a reduction in nitric oxide synthesis.[47,48] These effects, coupled with direct tubular toxicity of iodinated radiocontrast, lead to overt acute tubular necrosis and CI-AKI.

Immune-mediated mechanisms have also been implicated in the development of CRS type 1.[49,50] Evidence has suggested that an increased number of proinflammatory cytokines, a higher rate of apoptosis, and monocyte reprogramming have a pathogenic role in AKI.[51-53] It has been recently demonstrated that plasma-induced apoptosis, capsase-3 and 8 activities, and interleukin-6 levels were significantly higher in CRS type 1 patients when

compared with healthy controls and with patients with AHF but without kidney impairment.[54,55] However, the specific role of these cytokines in the causation of AKI in the setting of AHF remains to be elucidated.

CRS Type 3

The mechanisms underlying CRS type 3 are not clearly understood, but two general categories of effects have been proposed: direct effects of AKI on the heart and effects of AKI on remote organ function with indirect effects on the heart.[56] AKI triggers activation of the innate and adaptive immune systems, and in animal models of bilateral kidney ischemia increased levels of tumor necrosis factor α (TNF-α), interleukin-1, and intracellular adhesion molecule-1 (ICAM-1) mRNA were found in the heart after 48 hours of AKI and were accompanied by evidence of cardiac cell apoptosis and functional changes on echocardiography.[57,58]

Physiologic functions of the kidney are compromised during AKI, leading to dangerous complications that indirectly affect the heart, including fluid overload contributing to the development of edema, cardiac overload, hypertension, pulmonary edema, and myocardial dysfunction; hyperkalemia and other electrolyte imbalances that can be implicated in the development of arrhythmias; acidemia that disturbs myocyte metabolism and contributes to pulmonary vasoconstriction, increased afterload for the right ventricle, and has a negative inotropic effect; and accumulation of uremic toxins that depress myocardial contraction.[56] In addition, uremia is characterized by increased oxidative stress and inflammation that aggravates HF.[35]

Furthermore, kidney and heart can activate RAAS and the sympathetic nervous system. These two systems interact and potentiate each other, contributing to perpetuate volume overload, increased sympathetic tonus, and angiotensin II release with the final deleterious effects on heart including myocyte apoptosis, hypertrophy, and focal necrosis.[59]

Prevention and Management

CRS is an end result of the interaction between complex pathogenic factors, and once the syndromes set in, they are difficult to abort and are often not reversible in many cases. Most importantly, they are associated with adverse outcomes, even if the AKI episode is transient.[16,19] The pathophysiology of CRS also highlights the importance of limited organ reserve to recover from insults/injury due to the chronically damaged nature of the organs in the disease process. Thus, prevention of CRS is paramount in clinical practice with an aim to identify and avoid precipitating factors as well as to use measures to maintain optimal functioning of the diseased heart and kidney. This may involve multimodality and multidisciplinary preventive strategies, working via diverse therapeutic targets. Apart from pharmacological measures, some nonpharmacological and general preventive measures have to be reinforced across the whole spectrum of CRS. These include weight monitoring and management, smoking cessation, exercise, diet and nutrition, and improving compliance to pharmacological treatment.

Although standard evidence-based guidelines currently exist for management of AHF[60,61] and ACS,[62-64] and more recently for AKI,[10] there are no clear recommendations for the management of CRS types 1 and 3.[65] The multitude of pathophysiological interactions and their complexity render the management of CRS challenging. Only selected key aspects of kidney-related management will be reviewed here.

CRS Type 1

Improving the natural history of CHF and avoiding acute decompensation are the cornerstones of prevention in CRS type 1.[66] Strategies for prevention in these patients should follow those recommended by the ACC/AHA for stage A and B HF.[67] These include coronary artery disease risk factor modification and avoidance of medications that may precipitate salt and water retention, including nonsteroidal anti-inflammatory agents and thiozolidinediones. More importantly, use of RAAS antagonists and β-blockers (BBs) should be optimized appropriately. In patients with CKD, "therapeutic nihilism" should be avoided, and efforts must be made to cautiously introduce these cardioprotective agents, with the knowledge that close monitoring of kidney function will be needed.

Outpatient pharmacologic therapy of CHF needs to be individualized, reviewed frequently, and titrated against the patient's status regularly to avoid episodes of acute decompensation. In a recent meta-analysis of 14 trials involving 4264 patients, the use of remote telephone monitoring to ensure compliance and monitoring has shown to decrease hospitalization by 21% and all-cause mortality by 20%.[68] The use of biomarkers may further enhance telemedicine.[69] In a proposed telemedicine algorithm, patients are monitored on an outpatient basis with regular weight monitoring. When patients report a weight gain of 3-5 lb with HF symptoms, diuretic dose is to be adjusted and optimized via telephone advice. In patients who report a weight gain of 3-5 lb but without any overt signs of HF, brain natriuretic peptide (NP) is measured. The diuretic dose is then titrated based on changes in NP levels from baseline to achieve avert further volume overload.

Another mainstay of prevention is to recognize patients at risk for CRS. Patients who develop CRS type 1 are generally older, have a history of previous hospitalizations for HF or myocardial infarction, and often have baseline kidney dysfunction and hypertension. Risk

Table 2. Renoprotective Strategies in Patients at High-Risk for AKI or With AKI

General	Higher acuity monitoring (fluid balance, urine output, creatinine, blood pressure, cardiac function)
	Accurate evaluation of volume status (clinical and biomarker evaluation, bioimpedance analysis)
	Hold ACE inhibitors/ARB as appropriate
	Optimize volume status and perfusion pressure
	Adjust diuretic doses
	Pharmacovigilance (drug monitoring/dosing, avoiding nephrotoxins, attention to drug interaction)
AHF	Initial use of vasodilators, including nitrates, hydralazine, and nesiritide (in AHF)
CI-AKI	Consider alternative imaging methods to radiocontrast procedures
	Volume optimization with intravenous isotonic sodium chloride or sodium bicarbonate solutions prior to contrast procedure
	Minimize volume of radiocontrast media
	Iso- or low osmolar contrast media
	Consider oral *N*-acetylcysteine
ICU	Use isotonic crystalloids rather than colloids as initial management for intravascular volume expansion in the absence of hemorrhagic shock
	Use of vasopressors in conjunction with fluids
	Protocol-based management of hemodynamic and oxygenation parameters

Adapted from References.[10,102]

prediction scores for AKI have been published for AHF,[24] for CI-AKI after percutaneous coronary intervention[70] and after cardiac surgery,[71] and in hospitalized patients,[72] among others. Such scoring systems can be used to recognize preemptively the patients at a high intrinsic risk of developing acute kidney or cardiac complications. The use of biomarkers, such as the NPs, troponins, and novel kidney biomarkers may further enhance risk prediction, in addition to the clinical risk scores. These CRS biomarkers are extensively reviewed elsewhere.[73] Renoprotective measures can then be selectively instituted in high-risk patients with the aim of reducing the risk of acute CRS (Table 2).

In terms of management, diuretics have remained the cornerstone of treatment for AHF over the years and are used to treat signs and symptoms due to sodium and water retention.[36,37] However, loop diuretics predispose patients to electrolyte imbalance and hypovolemia, which in turn lead to neurohormonal activation and AKI. Furthermore, it is well-known that diuretic braking phenomena exist and postdiuretic sodium retention may further decrease responsiveness to diuretics, especially among patients with CKD. Therefore, aggressive diuresis may be needed to achieve clinical goals but may lead to undesirable consequences.

The optimal regimen for diuretics remains unclear. Continuous intravenous infusion of diuretics has traditionally been considered more effective than bolus in severe AHF.[74,75] However, in the recent DOSE-AHF randomized trial, there were no significant differences in patients' symptoms or in the change in kidney function when diuretic therapy was administered by bolus as compared with continuous infusion, or at a high dose (2.5 times the previous outpatient oral dose) as compared with a low dose (equivalent to the previous oral dose).[76] The high-dose strategy was associated with greater diuresis and more favorable outcomes in some secondary measures but also with transient worsening of kidney function (23% vs 14% in low-dose, $p = 0.04$). This is an important caveat. At least two studies, one in AHF[16] and another in the ACS,[19] have shown that the risk of poor outcome (death and rehospitalization) persisted regardless of whether CRS type 1 was transient or sustained. It is likewise important to note that patients with sCr greater than 3 mg/dL were excluded from this study. Such patients are more likely to need higher doses of furosemide and are more susceptible to develop CRS type 1 during hospitalization for AHF.

In addition to risk prediction, biomarkers can be used to monitor therapy and avoid overdiuresis. NP-guided therapy has been shown to be superior to symptom-guided therapy alone during hospitalization for AHF.[69,77,78] It has also been suggested that novel kidney biomarkers, such as neutrophil gelatinase- associated lipocalin and others, could potentially provide a biomarker "warning" that will trigger the physician to modify or suspend diuretic therapy and potentially avoid full-blown AKI, although this approach has not yet been studied in trials.[79] Furthermore, bioelectrical impedance analysis is a reliable and simple method to assess fluid status and fluid distribution in HF patients.[80] These methods provide more objective estimates of volume status in such patients. Used in conjunction with standard clinical assessment and biomarkers such as the NPs, bioimpedance analysis may be useful in guiding pharmacologic and ultrafiltration (UF) therapies and subsequently restoring such patients to a euvolemic or optivolemic state.[37,80]

UF is a potentially attractive alternative to loop diuretics for the management of fluid overload in patients with AHF and worsening kidney function. The UNLOAD trial, in which 200 patients were randomized to UF or intravenous diuretics, demonstrated that in AHF, UF safely produced greater weight and fluid removal

than intravenous diuretics, reduced 90-day resource utilization for HF, and was an effective alternative therapy.[81] The role of UF as a rescue therapy in patients with AHF and CRS will be compared with stepped pharmacologic care in the ongoing CARRESS-HF trial (see addendum below).[82]

The beneficial effects of ACE inhibitors, ARBs, aldosterone antagonists, and BBs in HF and ACS are well recognized.[40,41,43,45,83–87] However, the administration of BBs in patients with CRS type 1 merits great caution and generally should be avoided until the patients have been stabilized. This is because in such situations, maintenance of cardiac output is achieved via activation of the sympathetic nervous system and reflex tachycardia. Blunting of this compensatory response can thus precipitate cardiogenic shock.[88] Furthermore, aldosterone antagonist therapy is associated with a small but significant risk of severe hyperkalemia. Careful monitoring is therefore essential, particularly in patients with CKD. Vasodilators including nitroglycerin, isosorbide dinitarte, nitroprusside, and hydralazine have been used in the management of CRS especially in situations in which ACE inhibitors/ARBs may be contraindicated.[89] Evidence regarding the potential kidney-preserving effects of nesiritide is mixed, and it is not currently recommended for the prevention of AKI.[10]

CRS Type 3

In an analogous manner, optimized management of CKD as per established guidelines[90] and attention to potential AKI triggers are important in the prevention on CRS type 3. As noted above, appropriate renoprotective strategies specific for the clinical situation can be implemented in high-risk patients (Table 2). For example, an important factor contributing to kidney dysfunction in AHF and ACS is the administration of radiocontrast for imaging and procedures. Appropriate prophylaxis should be done to avoid CI-AKI.[10,91] In critically ill patients and in patients who undergo high-risk surgery, protocol-based management of hemodynamic and oxygenation parameters are recommended for the prevention of AKI.[92,93] These include the use of isotonic crystalloids rather than colloids as initial management for intravascular volume expansion in the absence of hemorrhagic shock and the appropriate use of vasopressors in conjunction with fluids.[10] Several pharmacologic strategies have shown promise in animal and/or early clinical studies, including loop diuretics, mannitol, low-dose dopamine, fenoldopam, atrial NP, and recombinant human insulin-like growth factor-1. To date none have been shown to provide consistent benefit for the prevention or attenuation of AKI, and are currently not recommended by consensus AKI guidelines.[10,94] Likewise, it is not recommended to select off-pump coronary artery bypass graft surgery for the sole purpose of reducing postoperative AKI.[10]

Although clinical models are in use for prediction of adverse cardiovascular outcomes after acute cardiac events (eg, after ACS[95-97]), there are currently no validated models for predicting the acute cardiac events themselves. In view of this knowledge gap, an important

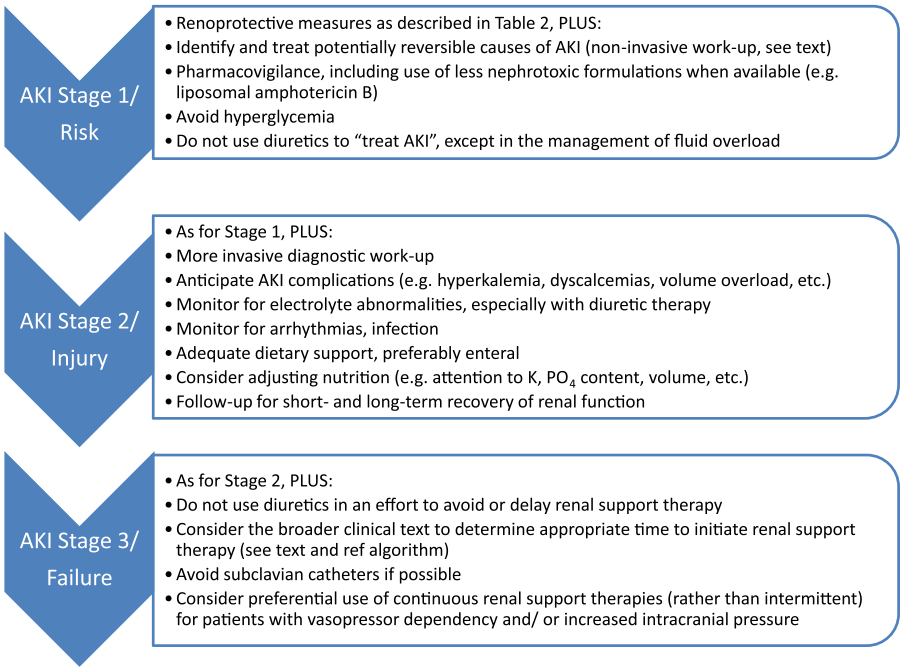


Figure 3. Supportive management in patients with established AKI. Modified with permission from Chuasuwan and Kellum [56] and the KDIGO group.[10]

research agenda would be to include acute and chronic cardiovascular events as outcomes in studies focused on AKI and to develop such models for external validation.

In the patient who already has established AKI, stage-based management of CRS type 3 has been proposed.[56] These are summarized in Figure 3. It is important to establish a diagnosis as soon as possible. Context-specific biomarkers (for example, brain NP and NT-pro-brain NP for HF; bilirubin and hepatic enzymes for hepatic failure; procalcitonin, endotoxin activity assay, and cultures for sepsis; and imaging and other studies [eg, urine sediment]) should be used to accurately establish the etiology of AKI. Moreover, it is important to search for reversible hemodynamic components and potential direct nephrotoxins. In milder stages of AKI (eg, AKIN Stage 1, RIFLE Risk), a noninvasive workup may be adequate. However, in more severe AKI, more invasive evaluation, including kidney biopsy, may be indicated. The previously described renoprotective measures (Table 2) should continue to be implemented in the AKI patient. In a prospective controlled nonrandomized intervention study, these relatively simple measures, recommended during the course of a prompt one-time nephrology consult within 18 hours of fulfilling AKI criteria, was associated with a lower peak sCr.[98] However, there were no cardiac endpoints described in this study. Electrolyte abnormalities, such as hypokalemia, hyopmagnesemia, and dysnatremias, are frequently encountered during diuretic therapy[36] and should be closely monitored.

The most common pathophysiology of acute cardiac decompensation in AKI is sodium and water retention. Hence, in AKI, a prompt aggressive avoidance of hypervolemia may avoid cardiac decompensation.[99,100] Moreover, uremic changes and acid-base and electrolyte abnormalities (such as metabolic acidosis) exhibit adverse consequences on cardiac contractility and its responsiveness to catecholamines. Electrolyte disturbances, such as hyperkalemia and hypokalemia, should be corrected to prevent arrhythmias with undesirable hemodynamic effects. Correction of the abnormal milieu in AKI with timely and appropriate interventions, including renal support therapy, may avert these complications.[101]

Conclusions

In summary, CRS is a complex and multidimensional entity that is commonly encountered in clinical practice but has a significant effect on morbidity and mortality. It is classified into five subtypes based on the primary organ dysfunction, whether heart ("cardiorenal" syndromes) or kidney ("renocardiac" syndromes) and on whether the organ dysfunction is acute or chronic. Of particular interest to the critical care specialist are CRS type 1 (acute CRS) and type 3 (acute renocardiac syndrome). Both subtypes are encountered in high-acuity medical units; in particular, CRS type 1 is commonly seen in the coronary care unit and cardiothoracic ICU. Preventive strategies in general for all patients with CKD and cardiac diseases, including HF and especially those in high-risk patients, will help decrease the incidence of acute deterioration of organ function. The management of these acute CRS subtypes is challenging because of the multitude and complexity of pathophysiological interactions between heart and kidney. Although standard evidence-based guidelines currently exist for management of AHF, ACS, and AKI, at present there are no clear recommendations for the management of CRS types 1 and 3.

Addendum: The CARRESS-HF study has been published.[103] The use of a stepped pharmacologic-therapy algorithm was superior to a strategy of ultrafiltration for the preservation of renal function at 96 hours, with a similar amount of weight loss with the two approaches. Ultrafiltration was associated with a higher rate of adverse events.

References

1. Ledoux P. Cardiorenal syndrome. *Avenir Med.* 1951;48:149-153.
2. Molls RR, Rabb H. Limiting deleterious cross-talk between failing organs. *Crit Care Med.* 2004;32:2358-2359.
3. Ronco C, McCullough P, Anker SD, et al. Cardio-renal syndromes: Report from the consensus conference of the Acute Dialysis Quality Initiative. *Eur Heart J.* 2010;31:703-711.
4. Bagshaw SM, Cruz DN, Aspromonte N, et al. Epidemiology of cardio-renal syndromes: Workgroup statements from the 7th ADQI Consensus Conference. *Nephrol Dial Transplant.* 2010;25: 1406-1416.
5. Cruz DN, Bagshaw SM. Heart-kidney interaction: Epidemiology of cardiorenal syndromes. *Int J Nephrol.* 2010;2011:351291.
6. Jose P, Skali H, Anavekar N, et al. Increase in creatinine and cardiovascular risk in patients with systolic dysfunction after myocardial infarction. *J Am Soc Nephrol.* 2006;17:2886-2891.
7. de Silva R, Nikitin NP, Witte KK, et al. Incidence of renal dysfunction over 6 months in patients with chronic heart failure due to left ventricular systolic dysfunction: Contributing factors and relationship to prognosis. *Eur Heart J.* 2006;27:569-581.
8. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure—Definition, outcome measures, animal models, fluid therapy and information technology needs: The Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care.* 2004;8:R204-R212.
9. Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care.* 2007;11:R31.
10. KDIGO Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int Suppl.* 2012;2:1-115.
11. Nohria A, Hasselblad V, Stebbins A, et al. Cardiorenal interactions: Insights from the ESCAPE trial. *J Am Coll Cardiol.* 2008;51:1268-1274.
12. Krumholz HM, Chen YT, Vaccarino V, et al. Correlates and impact on outcomes of worsening renal function in patients > or =65 years of age with heart failure. *Am J Cardiol.* 2000;85:1110-1113.
13. Gottlieb SS, Abraham W, Butler J, et al. The prognostic importance of different definitions of worsening renal function in congestive heart failure. *J Card Fail.* 2002;8:136-141.
14. Smith GL, Vaccarino V, Kosiborod M, et al. Worsening renal function: What is a clinically meaningful change in creatinine during hospitalization with heart failure? *J Card Fail.* 2003;9:13-25.

15. Cowie MR, Komajda M, Murray-Thomas T, Underwood J, Ticho B. Prevalence and impact of worsening renal function in patients hospitalized with decompensated heart failure: Results of the prospective outcomes study in heart failure (POSH). *Eur Heart J.* 2006;27:1216-1222.
16. Logeart D, Tabet JY, Hittinger L, et al. Transient worsening of renal function during hospitalization for acute heart failure alters outcome. *Int J Cardiol.* 2008;127:228-232.
17. Metra M, Nodari S, Parrinello G, et al. Worsening renal function in patients hospitalised for acute heart failure: Clinical implications and prognostic significance. *Eur J Heart Fail.* 2008;10: 188-195.
18. Goldberg A, Hammerman H, Petcherski S, et al. Inhospital and 1-year mortality of patients who develop worsening renal function following acute ST-elevation myocardial infarction. *Am Heart J.* 2005;150:330-337.
19. Latchamsetty R, Fang J, Kline-Rogers E, et al. Prognostic value of transient and sustained increase in in-hospital creatinine on outcomes of patients admitted with acute coronary syndrome. *Am J Cardiol.* 2007;99:939-942.
20. Newsome BB, Warnock DG, McClellan WM, et al. Long-term risk of mortality and end-stage renal disease among the elderly after small increases in serum creatinine level during hospitalization for acute myocardial infarction. *Arch Intern Med.* 2008;168: 609-616.
21. Parikh CR, Coca SG, Wang Y, Masoudi FA, Krumholz HM. Long-term prognosis of acute kidney injury after acute myocardial infarction. *Arch Intern Med.* 2008;168:987-995.
22. Marenzi G, Assanelli E, Campodonico J, et al. Acute kidney injury in ST-segment elevation acute myocardial infarction complicated by cardiogenic shock at admission. *Crit Care Med.* 2010;38:438-444.
23. Amin AP, Spertus JA, Reid KJ, et al. The prognostic importance of worsening renal function during an acute myocardial infarction on long-term mortality. *Am Heart J.* 2010;160:1065-1071.
24. Forman DE, Butler J, Wang Y, et al. Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. *J Am Coll Cardiol.* 2004;43:61-67.
25. Killip T III, Kimball JT. Treatment of myocardial infarction in a coronary care unit. A two year experience with 250 patients. *Am J Cardiol.* 1967;20:457-464.
26. Butler J, Forman DE, Abraham WT, et al. Relationship between heart failure treatment and development of worsening renal function among hospitalized patients. *Am Heart J.* 2004;147: 331-338.
27. Laskey WK, Jenkins C, Selzer F, et al. Volume-to-creatinine clearance ratio: A pharmacokinetically based risk factor for prediction of early creatinine increase after percutaneous coronary intervention. *J Am Coll Cardiol.* 2007;50:584-590.
28. Damman K, Navis G, Voors AA, et al. Worsening renal function and prognosis in heart failure: Systematic review and meta-analysis. *J Card Fail.* 2007;13:599-608.
29. Krotkiewski A, Sicinski A. Effect of electrolyte disorders on the ECG curve and so-called PAP (positive after-potential) in renal insufficiency. *Pol Arch Med Wewn.* 1961;31:829-836.
30. Kechker MI, Kulakov GP, Seisembekov TZ. ECG changes in patients with acute renal insufficiency under hemodialysis treatment. *Kardiologiia.* 1971;11:66-70.
31. Liano F, Junco E, Pascual J, Madero R, Verde E. The spectrum of acute renal failure in the intensive care unit compared with that seen in other settings. The Madrid Acute Renal Failure Study Group. *Kidney Int Suppl.* 1998;66:S16-S24.
32. Liano F, Pascual J. Epidemiology of acute renal failure: A prospective, multicenter, community-based study. Madrid Acute Renal Failure Study Group. *Kidney Int.* 1996;50:811-818.
33. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. *J Am Coll Cardiol.* 2008;52:1527-1539.
34. Liang KV, Williams AW, Greene EL, Redfield MM. Acute decompensated heart failure and the cardiorenal syndrome. *Crit Care Med.* 2008;36:S75-S88.
35. Bongartz LG, Cramer MJ, Doevendans PA, Joles JA, Braam B. The severe cardiorenal syndrome: 'Guyton revisited'. *Eur Heart J.* 2005; 26:11-17.
36. Aspromonte N, Cruz DN, Valle R, et al. Metabolic and toxicological considerations for diuretic therapy in patients with acute heart failure. *Expert Opin Drug Metab Toxicol.* 2011;7:1049-1063.
37. Aspromonte N, Cruz DN, Valle R, Ronco C. Management and monitoring of haemodynamic complications in acute heart failure. *Heart Fail Rev.* 2011;16:575-581.
38. Ellison DH. Diuretic therapy and resistance in congestive heart failure. *Cardiology.* 2001;96:132-143.
39. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J.* 2012;33:1787-1847.
40. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. *N Engl J Med.* 1987;316:1429-1435.
41. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. *N Engl J Med.* 1991;325:293-302.
42. Packer M, Poole-Wilson PA, Armstrong PW, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. *Circulation.* 1999;100:2312-2318.
43. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med.* 1999;341:709-717.
44. Zannad F, McMurray JJ, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med.* 2011;364:11-21.
45. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med.* 2001;345:1667-1675.
46. McMurray JJ, Ostergren J, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: The CHARM-Added trial. *Lancet.* 2003;362:767-771.
47. Tumlin J, Stacul F, Adam A, et al. Pathophysiology of contrast-induced nephropathy. *Am J Cardiol.* 2006;98:14K-20K.
48. McCullough PA. Contrast-induced acute kidney injury. *J Am Coll Cardiol.* 2008;51:1419-1428.
49. Rabb H. Immune modulation of acute kidney injury. *J Am Soc Nephrol.* 2006;17:604-606.
50. Burne-Taney MJ, Rabb H. The role of adhesion molecules and T cells in ischemic renal injury. *Curr Opin Nephrol Hypertens.* 2003;12:85-90.
51. Lee DW, Faubel S, Edelstein CL. Cytokines in acute kidney injury (AKI). *Clin Nephrol.* 2011;76:165-173.
52. Havasi A, Borkan SC. Apoptosis and acute kidney injury. *Kidney Int.* 2011;80:29-40.
53. Silva S, de Cal M, Cruz D, et al. Oxidative stress and 'monocyte reprogramming' in septic patients with acute kidney injury requiring CRRT. *Blood Purif.* 2008;26:188-192.
54. Virzi GM, Torregrossa R, Cruz DN, et al. Cardiorenal syndrome type 1 may be immunologically mediated: A pilot evaluation of monocyte apoptosis. *Cardiorenal Med.* 2012;2:33-42.
55. Virzi G, Cruz DN, Bolin C, et al. Immunomediated mechanisms of organ damage in cardiorenal syndrome type 1. *Eur Nephrol.* 2012;6:25-29.

56. Chuasuwan A, Kellum JA. Cardio-renal syndrome type 3: Epidemiology, pathophysiology, and treatment. *Semin Nephrol.* 2012;32: 31-39.
57. Kelly KJ. Distant effects of experimental renal ischemia/reperfusion injury. *J Am Soc Nephrol.* 2003;14:1549-1558.
58. Kinsey GR, Li L, Okusa MD. Inflammation in acute kidney injury. *Nephron Exp Nephrol.* 2008;109:e102-e107.
59. Jackson G, Gibbs CR, Davies MK, Lip GY. ABC of heart failure. *Pathophysiol BMJ.* 2000;320:167-170.
60. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail.* 2012;14:803-869.
61. Jessup M, Abraham WT, Casey DE, et al. 2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation.* 2009;119:1977-2016.
62. Hamm CW, Bassand JP, Agewall S, et al. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the Management of Acute Coronary Syndromes (ACS) in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J.* 2011;32:2999-3054.
63. Jneid H, Anderson JL, Wright RS, et al. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non-ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2012;60:645-681.
64. Steg PG, James SK, Atar D, et al. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology (ESC). *Eur Heart J.* 2012;33:2569-2619.
65. Davenport A, Anker SD, Mebazaa A, et al. ADQI 7: The clinical management of the Cardio-Renal syndromes: Work group statements from the 7th ADQI Consensus Conference. *Nephrol Dial Transpl.* 2010;25:2077-2089.
66. McCullough PA, Haapio M, Mankad S, et al. Prevention of cardiorenal syndromes: Work group statements from the 7th ADQI Consensus Conference. *Nephrol Dial Transpl.* 2010;25:1777-1784.
67. Hunt SA. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). *J Am Coll Cardiol.* 2005;46:e1-e82.
68. Clark RA, Inglis SC, McAlister FA, Cleland JG, Stewart S. Telemonitoring or structured telephone support programmes for patients with chronic heart failure: Systematic review and meta-analysis. *BMJ.* 2007;334:942.
69. Maisel A, Mueller C, Adams K, et al. State of the art: Using natriuretic peptide levels in clinical practice. *Eur J Heart Fail.* 2008;10: 824-839.
70. Mehran R, Aymong ED, Nikolsky E, et al. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: Development and initial validation. *J Am Coll Cardiol.* 2004;44:1393-1399.
71. Thakar CV, Arrigain S, Worley S, Yared JP, Paganini EP. A clinical score to predict acute renal failure after cardiac surgery. *J Am Soc Nephrol.* 2005;16:162-168.
72. Drawz PE, Miller RT, Sehgal AR. Predicting hospital-acquired acute kidney injury—A case-controlled study. *Ren Fail.* 2008;30: 848-855.
73. Cruz DN, Fard A, Clementi A, Ronco C, Maisel A. Role of biomarkers in the diagnosis and management of cardio-renal syndromes. *Semin Nephrol.* 2012;32:79-92.
74. Howard PA, Dunn MI. Aggressive diuresis for severe heart failure in the elderly. *Chest.* 2001;119:807-810.
75. Salvador DR, Rey NR, Ramos GC, Punzalan FE. Continuous infusion versus bolus injection of loop diuretics in congestive heart failure. *Cochrane Database Syst Rev.* 2005;3:CD003178.
76. Felker GM, Lee KL, Bull DA, et al. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med.* 2011;364: 797-805.
77. Valle R, Aspromonte N, Giovinazzo P, et al. B-type natriuretic peptide-guided treatment for predicting outcome in patients hospitalized in sub-intensive care unit with acute heart failure. *J Card Fail.* 2008;14:219-224.
78. Valle R, Aspromonte N, Carbonieri E, et al. BNP-guided therapy optimizes the timing of discharge and the medium term risk stratification in patients admitted for congestive heart failure. *Monaldi Arch Chest Dis.* 2007;68:154-164.
79. Ronco C, Cruz DN, Noland BW. Neutrophil gelatinase-associated lipocalin curve and neutrophil gelatinase-associated lipocalin extended-range assay: A new biomarker approach in the early diagnosis of acute kidney injury and cardio-renal syndrome. *Semin Nephrol.* 2012;32:121-128.
80. Aspromonte N, Cruz DN, Ronco C, Valle R. Role of bioimpedance vectorial analysis in cardio-renal syndromes. *Semin Nephrol.* 2012; 32:93-99.
81. Costanzo MR, Guglin ME, Saltzberg MT, et al. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J Am Coll Cardiol.* 2007;49:675-683.
82. Bart BA, Goldsmith SR, Lee KL, et al. Cardiorenal rescue study in acute decompensated heart failure: rationale and design of CARRESS-HF, for the Heart Failure Clinical Research Network. *J Card Fail.* 2012;18:176-182.
83. Weir RA, McMurray JJ, Puu M, et al. Efficacy and tolerability of adding an angiotensin receptor blocker in patients with heart failure already receiving an angiotensin-converting inhibitor plus aldosterone antagonist, with or without a beta blocker. Findings from the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM)-Added trial. *Eur J Heart Fail.* 2008;10:157-163.
84. Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med.* 1992;327:669-677.
85. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med.* 2001;344:1651-1658.
86. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet.* 1999;353:2001-2007.
87. Gensch C, Hoppe U, Bohm M, Laufs U. Late-breaking clinical trials presented at the American Heart Association Congress in Chicago 2010. *Clin Res Cardiol.* 2011;100:1-9.
88. Chen ZM, Pan HC, Chen YP, et al. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: Randomised placebo-controlled trial. *Lancet.* 2005;366:1622-1632.
89. Taylor AL, Ziesche S, Yancy C, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med.* 2004;351:2049-2057.
90. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease. *Am J Kidney Dis.* 2007;49:S12-S154.

91. Proceeding of the Contrast-Induced Nephropathy Consensus Panel, 17 September 2005, Paris, France. *Kidney Int Suppl.* 2006; 69:S1-S53.
92. Wiedemann HP, Wheeler AP, Bernard GR, et al. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med.* 2006;354:2564-2575.
93. Brienza N, Giglio MT, Marucci M, Fiore T. Does perioperative hemodynamic optimization protect renal function in surgical patients? A meta-analytic study. *Crit Care Med.* 2009;37:2079-2090.
94. Joannidis M, Druml W, Forni LG, et al. Prevention of acute kidney injury and protection of renal function in the intensive care unit. Expert opinion of the Working Group for Nephrology, ESICM. *Intensive Care Med.* 2010;36:392-411.
95. de Araujo Goncalves P, Ferreira J, Aguiar C, Seabra-Gomes R. TIMI, PURSUIT, and GRACE risk scores: Sustained prognostic value and interaction with revascularization in NSTE-ACS. *Eur Heart J.* 2005;26:865-872.
96. Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. *JAMA.* 2000;284:835-842.
97. Granger CB, Goldberg RJ, Dabbous O, et al. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med.* 2003;163:2345-2353.
98. Balasubramanian G, Al-Aly Z, Moiz A, et al. Early nephrologist involvement in hospital-acquired acute kidney injury: A pilot study. *Am J Kidney Dis.* 2011;57:228-234.
99. Bagshaw SM, Cruz DN. Fluid overload as a biomarker of heart failure and acute kidney injury. *Contrib Nephrol.* 2010; 164:54-68.
100. Bagshaw SM, Brophy PD, Cruz D, Ronco C. Fluid balance as a biomarker: Impact of fluid overload on outcome in critically ill patients with acute kidney injury. *Crit Care.* 2008;12:169.
101. Bagshaw SM, Cruz DN, Gibney RN, Ronco C. A proposed algorithm for initiation of renal replacement therapy in adult critically ill patients. *Crit Care.* 2009;13:317.
102. McCullough PA, Stacul F, Becker CR, et al. Contrast-Induced Nephropathy (CIN) Consensus Working Panel: Executive summary. *Rev Cardiovasc Med.* 2006;7:177-197.
103. Bart BA, Goldsmith SR, Lee KL, et al. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. *N Engl J Med.* 2012 Nov 6. [Epub ahead of print].