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Sub-Types and Therapeutic Management of the Cardiorenal Syndrome

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1. Introduction

Cardiorenal syndrome (CRS) describes the inter-relationship and complex pathophysiological processes by which dysfunction of either the heart or the kidneys is related to dysfunction in the other organ system. Historical definitions may have been overly simplistic; newer definitions have tried to capture the complex interactions and feedback processes which exist between the two organs. These definitions classify the CRS into five discrete categories, based on both the organ system in which the primary dysfunction occurs and the time course of disease development/progression.

The CRS is more common than many clinicians realize. Over one third of patients in heart failure (HF) registries have evidence of renal dysfunction, and a similar proportion of dialysis patients have symptoms of congestive HF or clinical evidence of left ventricular dysfunction (Adams et al., 2005; Stack & Bloembergen, 2001). Importantly, the presence of the CRS is a strong adverse prognostic marker in patients with either primary cardiac disease or primary renal disease.

While originally thought to reflect renal hypoperfusion secondary to low cardiac output, it is now understood that the CRS is underpinned by far more complex processes. From a hemodynamic standpoint, it seems likely that venous congestion is at least as important to the pathophysiology of disease progression as is low forward flow. Other contributing factors include activation of neurohormonal axes, including the sympathetic nervous system and the renin-angiotensin-aldosterone system, as well as oxidative injury and endothelial dysfunction (Bock & Gottlieb, 2010). More recently, it has become recognized that anemia may also be intimately involved in the process, both as a consequence and as a causative agent of the CRS. Finally, it is well recognized that many common risk factors for cardiovascular disease and for chronic kidney disease (CKD) co-exist in these patient cohorts.

Management of the CRS is challenging. Therapies for HF often cause worsening of renal function, while treatment of renal failure commonly involves fluid administration, which may precipitate disease decompensation among those with HF. Unfortunately, most large randomized trials in the HF population have excluded patients with elevated serum creatinine levels, and there is little evidence to guide therapy in this group of patients. Observational studies suggest that there may be a mortality benefit associated with the use

of standard HF medications, such as angiotensin converting enzyme inhibitors, angiotensin receptor blockers and beta blockers in patients with HF and CKD, regardless of glomerular filtration rate (GFR) (Berger et al., 2007; Cice et al., 2003).

Many novel therapies for HF have been introduced over recent years, several of which were appealing for treatment of the CRS, given the pathophysiological processes towards which they were directed. Unfortunately, natriuretic peptides, vasopressin antagonists, and adenosine antagonists have all failed to show meaningful clinical benefits in patients with HF (Hernandez, 2010; Konstam et al., 2007; Massie et al., 2010). Other approaches, particularly peripheral ultrafiltration, have shown more promise in this patient population (Costanzo et al., 2005).

2. Definitions and sub-types of the cardiorenal syndrome

Historically, the CRS is thought to have been due to impaired renal perfusion secondary to low cardiac output states or the result of HF therapies negatively impacting renal function. In 2004, the National Heart, Lung and Blood Institute defined CRS as a “state in which therapy to relieve heart failure symptoms is limited by further worsening in renal function” (National Heart, Lung and Blood Institute, 2004). By this paradigm, the heart was considered to be the central driving force behind impaired renal function in patients with HF.

Our understanding of the pathophysiology behind the CRS has evolved in the last number of years and there is increasing recognition of the complexity of interactions which exist between the heart and the kidneys, particularly when either or both organs are diseased. This organ cross talk is bidirectional in nature and the resultant dialogue is dependent on whether the heart or the kidney is the primary affected organ as well as the time course over which the associated pathophysiological changes may occur.

It is within this context, that newer definitions for the CRS have been proposed which recognize that either the heart or kidney may be the primary site of organ injury. A more comprehensive definition and classification schema for the CRS has the advantage of allowing clinicians to make a more accurate diagnosis which in turn informs our understanding of a given patient’s natural history, prognosis and optimal treatment strategy.

The definition and classification system for CRS introduced by Ronco and colleagues in 2008 (Ronco et al., 2008) is now widely considered to be the preferred mechanism for describing patients and the pathophysiological processes associated with CRS. Ronco and colleagues broadly define CRS as “a pathophysiological disorder of the heart and kidneys whereby acute or chronic dysfunction of one organ may induce acute or chronic dysfunction of the other.” Additionally, they characterize five sub-types of the CRS based on this definition. These are described and discussed below. It should be noted that CRS types 1-5 may frequently co-exist in a given patient, underscoring the complexity of interaction between the heart and kidney and the importance of appointing chronology to these processes.

2.1 Cardiorenal syndrome type 1 (acute cardiorenal syndrome)

Type 1 CRS is distinguished by an acute deterioration in cardiac function or acute cardiac injury, from any cause, that secondarily results in acute kidney injury (AKI).

Pathophysiologically, Type 1 CRS is characterized by decreased cardiac output with impaired renal perfusion as well as elevated central venous pressures and acute renal edema. Renal ischemia may be mediated by decreased oxygen delivery due to impaired myocardial contractile performance, elevated interstitial pressures in the renal medulla and by peripheral/systemic vasoconstriction which occurs as a compensatory mechanism in the face of low cardiac output.

Historically, decreased forward cardiac flow was thought to be the primary determinant for AKI in this context, however recent clinical trials have suggested this mechanism may not be as important in the development of CRS Type I as previously hypothesized. Specifically, data from ADHERE (Acute Decompensated Heart Failure National Registry) which included over 100,000 patients admitted to hospital in the United States with acute decompensated heart failure (ADHF) showed that <2% of patients had systemic hypotension, a surrogate for low cardiac output, while the vast majority of patients had symptoms/signs of volume overload (Adams et al., 2005). This is corroborated by the findings of the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) Trial in which 433 patients admitted to hospital with ADHF were randomized to pulmonary artery catheterization versus standard care to assess the efficacy of tailored haemodynamic therapy (Binanay et al., 2005). In the ESCAPE Trial, cardiac index was not associated with baseline renal function or deterioration in renal function, however right atrial pressure was weakly correlated with baseline creatinine and GFR (Nohria et al., 2008).

The impact of central venous pressures (CVP) on worsening renal function in the setting of ADHF has been receiving greater attention in recent years. Elevated CVP is more predictive of a decline in renal function than other relevant haemodynamic variables such as cardiac index, blood pressure and pulmonary capillary wedge pressure (Mullens et al., 2009). Moreover, elevated CVP predicts risk of re-hospitalization for HF and death suggesting that it is a potent prognosticator for poor outcomes and a potential target for therapy (Uthoff et al., 2011). Elevated intra-abdominal venous pressures have also been shown to have a similar relationship with GFR at baseline and changes in GFR with therapy (Bock & Gottlieb, 2010; S. E. Bradley & G. P. Bradley). This may be the result of a direct mechanical effect on renal blood flow or simply a reflection of elevated CVP.

Among patients with ADHF, activation of the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS) is a homeostatic mechanism intended to maintain intraglomerular perfusion pressures and preserve GFR. Paradoxically however, systemic vasoconstriction by these mechanisms increases cardiac afterload leading to further decline in cardiac output and renal blood flow. Additionally, these neurohormones have a maladaptive effect on the myocardium resulting in fibrosis and ventricular remodeling. Treatment with β -blockers is relatively contra-indicated in the face of an acute decompensation due to their negative inotropic effects and the relative dependence of cardiac output on heart rate in this patient population; therefore, SNS activation in CRS Type 1 may remain unchecked leading to ischemia of both renal and cardiac tissue beds.

Acute administration of RAAS inhibition may exacerbate renal injury in CRS Type 1 by reducing pressure in Bowman's capsule; this effect may be magnified in the presence of volume shifts associated with diuretics, which remains the mainstay of therapy. Moreover, diuretics may directly result in additional neurohormonal activation and there is now an

increasing body of literature suggesting that diuretics, in and of themselves, may be associated with worse outcomes in patients with ADHF independent of other relevant clinical variables. In a single centre retrospective analysis of 1354 patients admitted with ADHF, Eshaghian and colleagues (Eshaghian et al., 2006) demonstrated that patients requiring the highest doses of diuretics, stratified by quartiles, had higher rates of sudden death, death due to progressive pump failure and all cause mortality compared to patients in the lowest quartile of diuretic dose. This type of observation has fueled a growing interest in identifying alternate strategies for fluid management in the acute setting, independent of diuretic administration (see section 3.8).

Of particular concern among patients who present with the features of CRS Type 1 is the impact of diagnostic imaging and invasive cardiac procedures which may have an additional and direct toxic effect on the kidneys through a variety of mechanisms. Individuals who present with an acute deterioration in cardiac function will frequently require imaging or investigation to identify a precipitant or cause for their symptoms. Independently, percutaneous interventions and cardiac surgery impart a risk of AKI which is higher in patients who have pre-existing or concomitant acute renal insufficiency (Anderson et al., 1999; Best et al., 2002).

Upwards of 70% of patients admitted to hospital with ADHF will experience a rise in serum creatinine over the course of their admission (Gottlieb et al., 2002); this may be the result of therapies administered, either medical or invasive, or a consequence of the various pathophysiological processes which characterize CRS Type 1. Regardless of mechanism, worsening renal function portends a poor prognosis and is associated with higher mortality rates. (Gottlieb et al., 2002; Damman et al., 2007).

2.2 Cardiorenal syndrome type 2 (chronic cardiorenal syndrome)

Chronic HF leading to chronic kidney disease is the hallmark of CRS Type 2. The prevalence of CKD in HF cohorts has been variably reported depending on the patient population examined - e.g. hospitalized versus ambulatory patients. Further complicating our understanding of disease prevalence is the fact that early clinical trials of chronic HF excluded patients with established renal insufficiency and most did not determine glomerular filtration rate (GFR) which is of particular clinical importance given that HF is a disease of the elderly.

For example, the SOLVD (Studies of Left Ventricular Dysfunction) trials examined the impact of the angiotensin converting enzyme (ACE) inhibitor Enalapril on mortality and symptom development in patients with left ventricular dysfunction (The SOLVD Investigators, 1991; The SOLVD Investigators, 1992). While those with serum creatinine levels >2.0 mg/dL were excluded from the original trial, a retrospective analysis of study patients revealed at least moderate renal impairment (GFR < 60 ml/min) was present in 26% and 56% of participants in the prevention and treatment arms of the trial, respectively (Dries et al., 2000). Across the series of trials which composed the CHARM (The Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) Program, moderate renal impairment was detected in 36% of the 2680 study participants at baseline (Hillege et al., 2006).

Determining the prevalence of pre-existing CKD is particularly challenging among hospitalized HF patients. Some clinicians may attribute AKI at the time of HF

hospitalization solely to CRS Type 1 thereby underestimating the presence of concomitant CRS Type 2 in this cohort of patients. Novel biomarkers of AKI may help clinicians to decipher the relative contributions of CRS Type 1 versus CRS Type 2 in patients hospitalized for HF who have poor renal function upon presentation (Siew et al., 2011; Coca et al., 2008).

Regardless of cause, renal insufficiency in hospitalized HF patients appears to be relatively common; among those enrolled in ADHERE, the prevalence of at least moderate renal impairment, as determined by GFR, was greater than 60% at baseline (Heywood et al., 2007). This is in sharp contrast to initial reports from the same registry which suggested a prevalence rate of only 20% when a serum creatinine of 2.0 mg/dL was employed as a cut off (Adams et al., 2005). Calculation of GFR, therefore, is paramount to accurately identifying the burden of renal disease in all forms of CRS.

The true burden of pre-existing renal dysfunction among patients with HF was best characterized in a meta-analysis performed by Smith and colleagues. In their systematic review of the literature, approximately 80,000 hospitalized and non-hospitalized patients with HF were identified across 16 clinical trials. While 29% of patients were found to have moderate to severe renal impairment (GFR <53 mL/min or cystatin C of >1.56 mg/dL), 63% were found to have at least some degree of impaired kidney function. Moreover, these findings are likely to underestimate the true prevalence of renal insufficiency in HF populations given that 8 of the clinical trials included in the meta-analysis excluded patients on the basis of age or an elevated serum creatinine at baseline (Smith et al., 2006).

In the meta-analysis performed by Smith and colleagues, renal impairment at baseline conferred an increased risk of mortality at one year follow-up compared to patients with normal kidney function (Smith et al., 2006). The adjusted hazard ratio for patients with any renal impairment or moderate to severe renal impairment was 1.56 and 2.31 respectively. Excess risk was conferred in an incremental fashion with each 10 mL/min reduction in GFR correlating to a 7% increase in the risk of death. This observation is strengthened by similar findings across a spectrum of clinical trials in both hospitalized and ambulatory HF populations (Adams et al., 2005; Dries et al., 2000; Fonarow et al., 2005; Heywood et al., 2007; Hillege et al., 2006).

Many of the pathophysiological mechanisms which characterize CRS Type 1 are also implicated in the development of CRS Type 2, although many of these processes may occur slowly and over longer periods of time. For example, elevated central venous pressure is strongly associated with a decline in eGFR among patients with chronic HF (Damman et al., 2009; Firth et al., 1988); as described above, the same is true for patients with ADHF and CRS Type 1. Elevated CVP and secondarily an elevation in renal venous pressure may trigger a number of downstream events, including interstitial ischemia, neurohormonal activation and decreased responsiveness to natriuretic peptides which all combine to reduce GFR directly or indirectly (Damman et al., 2007; Bock & Gottlieb, 2010) in the setting of chronic HF. Chronically low cardiac output, particularly in combination with micro and macrovascular renal disease, may also contribute to fibrosis and structural changes in the kidney which result in impaired renal function.

RAAS activation occurs in both HF and CKD with an associated increase in Angiotensin II levels (AII). AII mediates oxidative injury and endothelial dysfunction through both the formation of reactive oxygen species and a decrease in nitric oxide bioavailability. Each of

these processes, in turn, can result in haemodynamic abnormalities at the level of the heart and kidney contributing to a decline in GFR (Bock & Gottlieb, 2010).

While neurohormonal inhibition and diuretic therapy are the mainstay of pharmacological HF management, these agents are also implicated in the worsening of GFR associated with CRS Type 2. ACE inhibitors and angiotensin receptor blockers (ARBs) result in systemic hypotension as well as efferent arteriolar vasodilatation with an associated decline in intraglomerular pressure and GFR. These effects may be magnified in the presence of concomitant diuretic use and relative intra-vascular volume depletion. The treatment of CRS is discussed in detail below.

The presence of anemia is common in patients with HF, an observation which is consistent across a number of clinical trials in the HF arena. A review of the literature suggests a prevalence rate of between 9-25% depending on the HF patient population studied and the cut-off criteria used to diagnose anemia (Virani et al., 2008; Al-Ahmad et al., 2001; Sharma et al., 2004; Anand et al., 2005; Horwich et al., 2002). Regrettably, many of these studies excluded patients based on renal function and therefore the relative contribution of low GFR to the development of anemia in these patient cohorts is lacking. Anemia in the presence of HF portends a poor prognosis with absolute haemoglobin (Hgb) levels correlating with 1 year survival; a precipitous increase in mortality is observed when Hgb drops below 120 g/L (Horwich et al., 2002; Ezekowitz et al., 2003).

The development of anemia in CRS Type 2 is likely multifactorial and underpinned by a number of processes occurring simultaneously; malnutrition, the formation of reactive oxygen species, cytokine release and erythropoietin (EPO) deficiency/resistance have all been implicated. When present, anemia may lead to further cardiac and renal dysfunction through impaired oxygen delivery and tissue hypoxia, neurohormonal activation, decreased renal blood flow and expansion of plasma volume with resultant cardiac remodeling (McCullough & Lepor, 2005). These mechanisms establish and propagate a vicious cycle of maladaptive processes which lead to worsening anemia, HF and kidney function as a net result.

2.3 Cardiorenal syndrome type 3 (acute renocardiac syndrome)

The RIFLE Criteria define acute kidney injury as a twofold increase in serum creatinine or a GFR decrease by 50 percent or urine output of <0.5 mL/kg per hour for 12 hours (Bellomo et al., 2004). By this definition, AKI is prevalent in nearly 9% of hospitalized patients (Uchino et al., 2006) with an associated 4-fold increased risk of mortality compared to patients without evidence of renal injury (Ricci et al., 2008). Much of that excess risk may be attributable to cardiac sequelae of AKI. CRS Type 3 characterizes this interaction and may be defined broadly as primary acute kidney injury, due to any number of causes, which secondarily leads to acute cardiac dysfunction.

A number of pathophysiological processes may be initiated as a consequence of AKI which have significant downstream cardiac effects. Biochemical abnormalities including hyperkalemia may pre-dispose to malignant cardiac arrhythmias and an increased risk of sudden cardiac death. Acidemia and uremia have direct myocardial depressant effects and may precipitate acute biventricular cardiomyopathy; these effects are exacerbated in the face of volume expansion.

Volume overload due to impaired solute and fluid clearance may also result in hypertension and pulmonary edema. Moreover, the resultant elevations in intra-cardiac filling pressures reduce the transmural perfusion gradient during diastole leading to sub-endocardial ischemia and overall worsening of ventricular function. Release of pro-inflammatory cytokines and reactive oxygen species in response to renal injury may result in endothelial dysfunction in addition to having direct toxic effects on the myocardium with resultant apoptosis and myocardial fibrosis.

Activation of the SNS and RAAS as a result of AKI may also lead to deleterious haemodynamic consequences including increased systemic vascular resistance and increased myocardial oxygen consumption, both of which lead to decreased cardiac output. While AII also causes left ventricular hypertrophy, ventricular remodeling and accelerates the development of atherosclerosis, these effects are likely of greater relevance in the setting of Chronic Renocardiac Syndrome (CRS Type 4).

2.4 Cardiorenal syndrome type 4 (chronic renocardiac syndrome)

CRS Type 4 describes a clinical scenario where primary CKD leads to structural and/or functional cardiac abnormalities which may be associated with clinically significant adverse cardiac events. Indeed, the presence of CKD portends a poor cardiac prognosis with the attributable risk of adverse events correlating in a step-wise manner to reduction in GFR (Go et al., 2004). Moreover, individuals with CKD have an accelerated natural history of their cardiac disease and are more likely to die from cardiac causes rather than progress to renal replacement therapy (Collins et al., 2008; Foley et al., 2005; Keith et al., 2004).

For example, in ALLHAT (The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) the risk of myocardial infarction (MI)/stroke, revascularization, death due to coronary disease and all forms of atherosclerotic vascular disease was increased as GFR decreased (Wali & Henrich, 2005). Among patients with CKD who experience an acute coronary syndrome, prognosis may also be stratified according to GFR. Shlipak and colleagues reviewed approximately 130,000 elderly patients hospitalized with an acute coronary syndrome and found a 2.5 fold increased risk of death between patients in the highest (CrCl > 0.92 mL/sec) and lowest (CrCl 0.17-0.54 mL/sec) tertile of creatinine clearance (Shlipak et al., 2002). Moreover, an analysis of nearly 120,000 patients from the Cooperative Cardiovascular Project suggested that renal function was a more accurate predictor of long term mortality post-MI than left ventricular systolic function, the presence of heart failure or prior MI (Smith et al., 2008). This relationship has been demonstrated in a multitude of clinical trials across a variety of cardiac cohorts and the observation between CKD and poor cardiac outcomes remains robust (Ronco et al., 2008).

There are many postulates as to the mechanisms underlying poor cardiac outcomes in patients with chronic renal dysfunction. It would appear that the burden of coronary artery disease and myocardial ischemia is greater in patients with CKD than those without (Ix et al., 2003). This may be due to a higher preponderance of traditional risk factors for coronary artery disease in this patient population (Muntner et al., 2005; Parikh et al., 2006) or simply that CKD, in and of itself, imparts increased risk of adverse cardiac events (Levey et al., 2003). In the Framingham Offspring Cohort, two or more traditional cardiovascular risk factors were identified in 73% of patients with CKD (GFR <60 mL/min) compared to 51.4 %

of participants without CKD. A statistically significant increase in hypertension and diabetes along with a trend towards increased dyslipidemia were more prevalent in the CKD cohort (Parikh et al., 2006). Existing data would suggest that CKD is independently associated with a higher risk for cardiovascular endpoints in affected patients; the magnitude of this excess risk, however, does not support elevating CKD to the level of a cardiovascular disease equivalent as is the case with diabetes or prior MI (Wattanakit et al., 2006).

Other potential pathophysiological processes involved in the development and acceleration of coronary atherosclerosis in patients with CKD include abnormalities of mineral metabolism leading to vascular calcification and endothelial dysfunction secondary to both chronic inflammation and EPO deficiency. Uremia, hypertension and increased vascular stiffness contribute to progressive left ventricular hypertrophy and diastolic dysfunction, which in time may progress to systolic dysfunction. Neurohormonal activation results in myocardial fibrosis and maladaptive ventricular remodelling which may hasten this process. In the presence of volume expansion, patients with either systolic or diastolic dysfunction remain at high risk for developing decompensated heart failure.

Observational trials very clearly demonstrate that those with CKD, as a result of actual or perceived contraindications, are less likely to receive efficacious and evidence based therapies compared to cohorts of patients with normal renal function (Al-Suwaidi et al., 2002; Parikh et al., 2006). An even more important observation is that those patients with CKD who do receive appropriate guideline based interventions have better outcomes (Shlipak et al., 2002); therapeutic prejudice of healthcare teams and providers in relation to patients with renal dysfunction is most certainly misplaced, particularly since this group of patients have a high burden of disease and therefore may receive the greatest degree of benefit from aggressive intervention.

2.5 Cardiorenal syndrome type 5 (secondary cardiorenal syndrome)

Secondary cardiorenal syndrome is the result of a systemic disorder leading to simultaneous cardiac and renal injury; each of these processes may be acute or chronic in nature and CRS Type 5 does not preclude involvement of other organs and tissue beds. Moreover, other sub-types of the CRS may exist concomitantly due to pre-existing co-morbidities.

The prevalence of CRS Type 5 overall has not been well described, primarily due to a paucity of data in this arena, however the frequency of cardiac and renal involvement for specific systemic disease states may be described in the literature. For example, myocardial injury in the absence of an acute coronary syndrome, as manifested by a positive troponin assay, is present in up to one-half of patients with sepsis admitted to a critical care unit (Amman et al., 2003). Similarly, AKI may occur in 70% of this patient population (Kim et al., 2011). Dysfunction of either or both organ systems portends a poor prognosis.

Connective tissue disease, sarcoidosis, amyloidosis, diabetes and sepsis are the most commonly referred to systemic process that may predispose to secondary CRS (Ronco et al., 2008). While a discussion of cardiac and renal involvement in each of these disease states is beyond the scope of this chapter, it is clear that definitive treatment must be focused at correcting the underlying pathophysiological process while providing supportive care for the heart and kidneys in the interim.

3. Management of the cardiorenal syndrome

Management of the CRS presents a challenge to the clinician. Treatment of HF with standard therapies often results in worsening of renal function. Moreover, most randomized clinical trials of HF therapies, including β -blockers, ACE inhibitors, ARBs and aldosterone antagonists, have excluded patients with significant renal dysfunction. Therefore, the results of these trials, most showing significant reductions in morbidity and mortality in the general HF population, may not be applicable to the CRS population. Observational studies and small randomized studies, however, have suggested that many of these drug classes may have similar benefit in patients with renal dysfunction (Berger et al., 2007; Cice et al., 2003). A number of novel strategies have been described that may offer specific benefit in the CRS population, although data from clinical trials have not always been encouraging.

Management of chronic CRS is overall similar to the management of HF in general, employing a combination of diuretics, inhibitors of the RAAS, and β -blockers. In the hospitalized patient with CRS and ADHF, diuretics remain a mainstay of therapy, but may be supplemented by additional therapies including novel pharmacologic agents, inotropic support, and ultrafiltration.

3.1 Diuretics

While fluid removal with diuretics is a cornerstone of HF management, diuretic resistance is highly prevalent in patients with decreased renal function, making this aspect of care for the patient with CRS particularly challenging. Furthermore, effective diuresis can result in further deterioration in renal function, particularly when the rate of fluid removal exceeds the rate of fluid movement from the extravascular space to the intravascular space, resulting in low effective circulating volume. Thus, two of the greatest obstacles in treating patients with CRS are overcoming diuretic resistance and effectively removing fluid without compromising renal function.

Loop diuretics (LD) such as furosemide act at the thick ascending limb of the loop of Henle, inhibiting the $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ cotransporter. LD are protein bound, preventing filtration at the glomerulus, but are actively secreted in the proximal tubule. Effective delivery to the loop of Henle requires effective delivery to the bloodstream (through intestinal absorption or direct intravenous administration), adequate renal blood flow, intact proximal tubule secretion, and delivery of tubular contents to the more distal nephron. There are therefore a number of mechanisms by which diuretic resistance may occur (Jentzer et al., 2010).

Delayed intestinal absorption is common in patients with HF, owing to intestinal wall edema. This can be most effectively overcome by using intravenous LD in patients who are markedly volume overloaded, and transitioning to oral administration once signs of congestion elsewhere (i.e. peripheral edema, venous congestion on chest X-ray) have resolved. Reduced renal blood flow (RBF) and GFR are also prevalent in patients with HF and CRS as a result of intrinsic renal dysfunction, decreased cardiac output, and alteration in glomerular haemodynamics by agents such as non-steroidal anti-inflammatory drugs (NSAIDs), ACE inhibitors, and ARBs. Avoiding agents such as NSAIDs, optimizing systemic hemodynamics, and increasing LD dose can help to overcome this aspect of resistance to LD. Similarly, proximal tubular secretion of LD is reduced in patients with CRS

because organic acids that accumulate in the uremic state compete for the same transporters; increased doses of LD may be required to overcome this problem.

Through intravascular volume depletion, LD may result in activation of the RAAS. This leads to increased sodium absorption by the proximal and distal tubule. This issue is compounded by the fact that post-diuretic rebound sodium avidity occurs between bolus doses of LD, negating much of the natriuretic benefit achieved. Strict dietary sodium restriction and administration of RAAS antagonists (i.e. ACE inhibitors and ARBs) may help to prevent this. Historically, it has been believed that continuous infusions of diuretics may also be effective in minimizing rebound sodium absorption; the recent DOSE (Diuretic Strategies in Patients with Acute Decompensated Heart Failure) trial suggests that there may be no difference in diuretic efficacy between intermittent intravenous bolus dosing and continuous infusions (Felker et al., 2011).

The “braking phenomenon” is a short-term effect, whereby the nephron becomes less sensitive to LD after an initial dose. This is thought to result from upregulation of the $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ cotransporter in the thick ascending loop of Henle. Higher doses of LD may be necessary to overcome this. With chronic LD administration, distal tubule hypertrophy occurs. This allows increased distal sodium reabsorption, tending to negate the inhibition of sodium reabsorption that has occurred in the loop of Henle.

A strategy of combination diuretic administration, with the addition of a thiazide diuretic such as metolazone 5-10 mg 30 minutes prior to LD administration can help to prevent sodium retention by this mechanism. Thiazides inhibit the NaCl cotransporter in the distal convoluted tubule. Caution is needed, however, as combination diuretic therapy can result in profound electrolyte abnormalities. Serum levels of potassium and magnesium must be closely monitored and infrequent metolazone dosing (i.e. three times per week) or co-administration of a potassium-sparing diuretic may be necessary to prevent life-threatening hypokalemia.

Finally, sodium and water retention may be upregulated in the distal nephron in patients with CRS, mediated by elevated levels of aldosterone and vasopressin, respectively. Administration of aldosterone antagonists or other potassium-sparing diuretics will minimize sodium retention in this situation; the new vasopressin antagonists have a role in preventing excessive absorption of free water (see section 3.6). Free water restriction may also be necessary in patients with refractory fluid overload or significant hyponatremia. An important caveat to the use of aldosterone antagonists in CRS is the risk of hyperkalemia in patients with renal impairment; these agents should generally be avoided in patients with $\text{GFR} < 30 \text{ mL/min}$.

Major drawbacks to the use of LD include neurohormonal activation, ototoxicity, electrolyte abnormalities (particularly hypokalemia and hypomagnesemia), dysrhythmias, and intravascular volume depletion with resultant worsening renal function and/or hypotension in patients who are preload-dependent or receiving concomitant vasodilator therapy.

A novel approach to diuretic use involves the co-administration of loop diuretics and hypertonic saline solution (HSS). Small studies in patients with ADHF have demonstrated that, compared to intravenous bolus loop diuretics with a low sodium diet, administration

of intermittent boluses of HSS with loop diuretics and moderate dietary sodium restriction resulted in more rapid diuresis, normalization of neurohormonal activity, shorter hospitalizations, and less renal dysfunction (Licata et al., 2003; Paterna et al., 2000). After discharge, these results were maintained by continuing moderate sodium restriction (<2.8 g/day) with strict fluid restriction (<1 L/day), resulting in fewer readmissions and improved survival compared to continued strict sodium (<2 g/day) and similar fluid restriction. The mechanism by which HSS provides these benefits is unclear, but may be related to the osmotic load drawing interstitial fluid into the intravascular space, leading to neurohormonal blockade, reduced vascular resistance, improved cardiac output, and reduced interstitial edema. In addition, the sodium load in the kidney may induce a sort of transient diabetes insipidus, resulting in rapid diuresis (Di Pasquale et al., 2007). Further research and larger scale studies are required to confirm the benefits of HSS in patients with CRS.

3.2 Renin-angiotensin-aldosterone system antagonists

Inhibitors of the renin-angiotensin system, including ACE inhibitors and ARBs have proven survival benefit in patients with left ventricular dysfunction (The SOLVD Investigators, 1991; The SOLVD Investigators, 1992), and have also been shown to slow the rate of decline of renal function in patients with diabetic chronic kidney disease (Lewis et al., 1993). It stands to reason, therefore, that these agents would be beneficial in the CRS, although large-scale clinical trials in the HF population have typically excluded patients with significant renal dysfunction.

The CHARM studies investigated the effects of candesartan compared with placebo in a broad population of patients with HF. Patients with serum creatinine >3.0 mg/dL were excluded, but among the study population, there was no statistically significant interaction between eGFR and treatment effect, suggesting a mortality benefit of ARBs in patients with HF and mild-to-moderate renal dysfunction that is equivalent to that seen in patients with HF and preserved renal function (Hillege et al., 2006). An analysis of CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study) which demonstrated a mortality benefit of enalapril compared to placebo in patients with HF, found a greater benefit in patients with baseline serum creatinine above the median (123 $\mu\text{mol/L}$) than in those with serum creatinine below the median (Swedberg et al., 1990). A retrospective analysis of the Minnesota Heart Survey stratified 4573 patients hospitalized with HF by GFR, and revealed that patients at all stages of CKD had reduced in-hospital mortality when an ACE inhibitor or ARB was used in hospital, and reduced one-year mortality when discharged on an ACE inhibitor or ARB (Berger et al., 2007). This same analysis, however, demonstrated that patients with severe renal dysfunction were far less likely to receive either agent than those with normal renal function.

In HF, elevated angiotensin II levels cause efferent arteriolar vasoconstriction, elevating glomerular filtration pressure and preserving GFR. Inhibition of this process with ACE inhibitors or ARBs may result in an initial decline in GFR, but in the long term protects the glomerulus from high filtration pressures and may help to preserve long-term renal function (Heywood, 2004). Although there appear to be benefits of using these agents in the CRS population, caution must be taken when initiating ACE inhibitors and ARBs in patients with renal dysfunction, particularly with regard to volume status and avoidance of NSAIDs.

Volume depletion increases the risk of significant renal dysfunction associated with ACE inhibitors and ARBs. Increases in creatinine of up to 30% are acceptable, and may identify a group of patients most likely to benefit from angiotensin inhibition (Koniari et al., 2010). HF patients who are unable to tolerate ACE inhibitor therapy because of hypotension, renal dysfunction, or hyperkalemia have a particularly high one-year mortality rate, in excess of 50% (Kittleson et al., 2003).

3.3 β -adrenergic receptor blockers

β -blockers are considered standard therapy in patients with HF and systolic dysfunction. They exert a number of beneficial effects, including prevention of ventricular arrhythmias, prevention of ventricular remodeling, reduction in myocardial oxygen demand, increased myocardial oxygen supply, and inhibition of other deleterious neurohormonal pathways. Their significant mortality benefit in patients with HF is well established through large clinical trials. Unfortunately, the majority of these studies excluded patients with significant renal dysfunction, but retrospective analyses of trials data have offered insight into the benefits in patients with mild-to-moderate renal impairment. COPENICUS (Carvedilol Prospective Randomized Cumulative Survival Study), for example, demonstrated a 35% reduction in the risk of death in patients with severe HF treated with carvedilol compared to placebo, but excluded patients with a serum creatinine greater than 2.8 mg/dL. Similarly, the CAPRICORN (Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction) trial showed a 23% reduction in all-cause mortality in patients with EF \leq 40% after myocardial infarction treated with carvedilol compared with placebo, but excluded patients with significant renal impairment (Dargie, 2001). A post-hoc analysis of individual patient data from these two trials, however, demonstrated that in patients with HF and mild-to-moderate CKD, carvedilol was safe and efficacious, associated with reductions in all-cause mortality, cardiovascular mortality, and HF hospitalization (Wali et al., 2011). CIBIS-II (The Cardiac Insufficiency Bisoprolol Study II) demonstrated a 34% reduction in mortality in patients with HF treated with bisoprolol compared to placebo, and excluded patients with serum creatinine \geq 300 μ mol/L (3.4 mg/dL) (CIBIS-II Investigators and Committees, 1999). A post-hoc analysis of this trial showed that although patients with GFR $<$ 60 mL/min had higher overall mortality than those with GFR \geq 60 mL/min, the benefit of bisoprolol was similar in both groups (Erdmann et al., 2001). The relative risk of mortality in the group with GFR $<$ 60 mL/min treated with bisoprolol compared to placebo was 0.66, and there was a non-significant trend towards an even greater benefit in the small number of patients with GFR $<$ 30 mL/min.

An analysis of MADIT-II (Multicenter Automatic Defibrillator Implantation Trial II), which demonstrated a 31% reduction in the risk of all-cause mortality with the addition of an implantable cardioverter-defibrillator to medical therapy in patients with ischemic cardiomyopathy and EF \leq 30%, examined the predictors of sudden cardiac death (SCD) in the subset of patients in the medical arm of the study with impaired renal function, defined as GFR \leq 75 mL/min. β -blocker therapy was a negative predictor of SCD, with a hazard ratio of 0.61 (Chonchol et al., 2007).

Smaller studies have examined the benefits of β -blocker therapy in patients with end-stage renal failure. In a non-randomized study of 134 patients with HF and either chronic renal impairment, anemia, or both, treatment with β -blockers for 12 months was associated with

improvement in both creatinine clearance and hemoglobin levels, while those patients who did not receive β -blockers had worsening renal function and anemia over the same time period (Khan et al., 2006). In patients with HF and normal renal function at baseline, lack of treatment with a β -blocker was associated with increased risk of developing renal failure over 20 years of follow-up (Tanaka et al., 2007). In hemodialysis patients with dilated left ventricles, treatment with metoprolol resulted in reduced ventricular dimensions, increased fractional shortening, and reduced levels of natriuretic peptides (Hara et al., 2001). A randomized trial of 114 hemodialysis patients with dilated cardiomyopathy showed that carvedilol, compared to placebo, was associated with improved ejection fraction, improved survival, and fewer HF hospitalizations (Cice et al., 2003). Although large-scale clinical trials in this population are lacking, the weight of evidence suggests that treatment with β -blockers in the CRS population is likely to be associated with reductions in mortality and morbidity.

3.4 Inotropic agents

Inotropic medications such as dobutamine and milrinone are frequently used in patients with ADHF, particularly in the setting of the CRS where low cardiac output is felt to be a major contributor to rapidly declining renal function. Both agents are vasodilating inotropes, but they have different mechanisms of action. Dobutamine is an adrenergic agonist that affects inotropy and chronotropy via β -1 activity and peripheral vasodilation via β -2 activity. Milrinone is an inhibitor of type III phosphodiesterase and results in increased intracellular cyclic adenosine monophosphate (cAMP). This, in turn, results in increased inotropy (without chronotropy) as well as peripheral vasodilation. Although both agents have attractive hemodynamic profiles in the treatment of CRS, evidence suggests that they should not be part of standard therapy in this condition. OPTIME-CHF (Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure) compared intravenous milrinone to placebo in patients with ADHF not requiring inotropic therapy for shock or other indications. There was no difference between the two groups in the primary endpoint of total number of days in hospital by 60 days after randomization. There was also no difference in the rate of progression of HF, but the patients treated with milrinone had higher rates of treatment failure, largely driven by higher rates of hypotension and atrial arrhythmias.

The ADHERE registry compared outcomes of patients with ADHF treated with vasodilating medications (nitroglycerin, nesiritide) and inotropic agents (dobutamine, milrinone). Even after adjustment for baseline variables including age, gender, blood pressure, BUN, creatinine, sodium, heart rate, and symptom severity, odds ratios for mortality between individual inotropes and individual vasodilators ranged from 1.45 to 2.17. Inotropic agents, therefore, are recommended by major society guidelines only for short-term use in patients with cardiogenic shock or refractory volume overload with diuretic resistance, and not recommended for routine use in hospitalized patients with ADHF. In addition, patients receiving these agents must be carefully monitored for hypotension and arrhythmias, and it should be recognized that the use of these agents is associated with a worse prognosis.

Dopamine is an endogenous catecholamine that binds dopamine receptors (D1-D5) as well as α and β adrenergic receptors with varying affinity depending on the dose administered. At low doses (2-5 mcg/kg/min), it primarily binds dopaminergic receptors and causes

vasodilation of renal, splanchnic, cerebral, and coronary vessels. At higher doses, β adrenergic effects dominate, resulting in positive inotropy and chronotropy as well as β adrenergic-mediated vasodilation, with progressively increasing α adrenergic activity at still higher doses resulting in vasoconstriction.

For many years the use of “renal-dose” dopamine was advocated in acute renal failure, the rationale being that dopamine in doses up to 5 mcg/kg/min in animals and healthy volunteers resulted in increased renal blood flow and natriuresis via selective dopamine receptor binding. In recent years this approach has fallen out of favor, as multiple retrospective and small prospective studies failed to convincingly demonstrate any benefit in terms of renal function or survival. A meta-analysis of 61 trials comparing low-dose dopamine to placebo or no treatment found that dopamine was associated with a 24% increase in urine output on day 1 but was not associated with reductions in mortality, need for renal replacement therapy, or adverse events (Friedrich et al., 2005). Only one of the 61 studies included patients with HF, and this study did not assess mortality; only three of the studies included patients who were receiving diuretics. More recently, data from the DAD-HF (Dopamine in Acute Decompensated Heart Failure) trial has been presented, comparing low-dose dopamine plus low-dose furosemide to high-dose furosemide alone in patients with ADHF. The two regimens were not associated with statistically significant rates of diuresis, but the patients receiving dopamine plus low-dose furosemide were less likely to develop worsening renal function (36% and 4% of patients in dopamine/furosemide and furosemide only groups, respectively, had >25% increase in serum creatinine). As more data become available regarding outcomes with low-dose dopamine in this specific population, “renal-dose” dopamine may turn out to be useful after all.

3.5 Vasodilators

Nesiritide, a synthetic B-type natriuretic peptide (BNP), has been used in the management of ADHF, particularly in patients at risk for worsening renal function with standard therapies. Like naturally occurring BNP, released from ventricular myocardium under conditions of increased wall stress, nesiritide is a vasodilator, causing both arterial and venous dilatation as well as mild diuresis. Its rapid onset of action, apparent neurohormonal benefits, and lack of need for invasive hemodynamic monitoring led to much initial enthusiasm for its use in ADHF, as well as FDA approval for this indication (Publication Committee for the VMAC Investigators, 2002). Use of this agent took a sharp decline, however, after meta-analyses suggested increased 30-day mortality and increased risk of renal failure with nesiritide (Hauptman et al., 2006; Sackner-Bernstein et al., 2005a; 2005b). The definitive randomized clinical trial, ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure), recently demonstrated that while nesiritide is safe with no increased risk of 30-day death or hospitalization or increased risk of renal failure, it offers no significant clinical benefit when added to standard therapy in patients with ADHF (Hernandez, 2010).

3.6 Vasopressin antagonists

Arginine vasopressin (AVP), a nonapeptide synthesized by the hypothalamus and released by the posterior pituitary gland in response to increased plasma osmolality or decreased plasma volume, binds to 3 distinct receptor subtypes (V1a, V1b, and V2). V1 receptors

mediate cardiac myocyte hypertrophy, vasoconstriction, and platelet aggregation. When AVP binds V2 receptors expressed in the renal collecting duct, the short-term result is increased translocation of vesicles containing aquaporin-2 (AQP2) water channels to the apical membrane of principal cells; in the long-term, AVP-V2 receptor binding results in the up-regulation of AQP2 protein expression. AQP2 mediates water transport across the apical membrane of the principal cell, resulting in urinary concentration and increased solute-free water retention (Schrier et al., 2009). AVP also stimulates urea reabsorption, resulting in an augmented medullary concentrating gradient and increased levels of blood urea nitrogen (Sands, 2003).

In HF and CRS, low cardiac output causes nonosmotic AVP release, leading to inappropriate water retention. Low serum sodium and elevated blood urea nitrogen are strong predictors of mortality in HF, and both are mediated, at least in part, by AVP activity in the kidney. Augmentation of cardiac output with vasodilator medications is associated with reductions in plasma AVP (Bichet et al., 1986). Early studies demonstrated effective water removal without worsening renal function (Gheorghide et al., 2007). Thus, the use of agents that interfere with AVP-mediated water retention has been an attractive concept in CRS. The SALT-1 and SALT-2 trials showed that tolvaptan, a selective oral V2 receptor antagonist, caused increases in serum sodium levels in patients with HF, cirrhosis, and the syndrome of inappropriate antidiuretic hormone (Schrier et al., 2006). Unfortunately, the randomized EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan) trial subsequently failed to demonstrate a mortality benefit or reduction in HF morbidity in patients hospitalized with HF treated with tolvaptan, despite sustained reductions in body weight with preserved renal function (Konstam et al., 2007). It seems, therefore, that vasopressin antagonists have little role in influencing clinical outcomes in patients hospitalized with HF and the CRS, although they may be useful in patients with hyponatremia that is difficult to manage with standard therapies. Additional studies are needed to further define the role of tolvaptan and other vasopressin antagonists in the outpatient setting.

3.7 Adenosine antagonists

Adenosine is a purine nucleoside breakdown product of adenosine triphosphate. It interacts with four main receptor subtypes: A1, A2a, A2b, and A3. With the exception of coronary vasodilatation and increased renal medullary blood flow, its cardiovascular and renal effects are largely mediated via the A1 receptor. Binding of adenosine to A1 receptors in the heart results in slowing of the heart rate and decreased atrial contraction. In the kidney, adenosine is released from the macula densa in response to sodium delivery to the distal nephron via tubuloglomerular feedback (TGF). Adenosine released through TGF acts on local A1 receptors, causing afferent arteriolar vasoconstriction and reduction in GFR as well as increased proximal tubular sodium reabsorption. Blockade of these receptors should, therefore, result in improved renal blood flow and GFR and decreased sodium and water reabsorption.

In the setting of CRS, loop diuretics cause increased sodium delivery to the distal tubule, making the role of adenosine particularly relevant in this population. Animal studies showed that rolofylline, a selective A1 receptor antagonist, caused increased urine flow and urinary sodium excretion without increasing potassium excretion and without affecting

either blood pressure or renal function, and protected against nephrotoxic medication-induced acute renal failure (Nagashima & Karasawa, 1996; Yao et al., 1994). A small clinical study supported this, demonstrating that the addition of rolofylline to diuretics in patients with volume overload and renal impairment resulted in an improvement in renal function and increased diuresis with reduced diuretic requirements (Givertz et al., 2007). Unfortunately, the PROTECT (Placebo-Controlled Randomized Study of the Selective A₁ Adenosine Receptor Antagonist Rolofoylline for Patients Hospitalized With Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function) study, which randomized 2033 patients with ADHF to intravenous rolofylline or placebo, failed to demonstrate any difference between groups in the primary endpoint of treatment success (moderate or marked improvement in dyspnea at 24 and 48 hours without treatment failure), treatment failure (death or readmission for HF by 7 days, persistent worsening renal failure, or worsening HF), or no change (Massie et al., 2010). There were no differences in the number of patients who developed renal impairment or in the secondary endpoint of death or rehospitalization for cardiac or renal causes at 60 days. The overall adverse event rates were similar between groups, although more patients in the rolofylline group had seizures, a known side effect of A₁ antagonists mediated via central nervous system A₁ receptors that regulate electrical excitability. Based on the lack of clinical efficacy, coupled with the increased risk of seizures, rolofylline is not recommended for the treatment of CRS.

Another intravenous selective A₁ antagonist, tonapofylline, was also investigated in Phase II clinical trials after preclinical studies and small human studies suggested effective natriuresis. The TRIDENT-1 (Safety and Tolerability of IV Tonapofylline in Subjects With Acute Decompensated Heart Failure and Renal Insufficiency) and POSEIDON (Oral BG9928 in Patients with Heart Failure and Renal Insufficiency) trials were both terminated early after review of interim safety data from TRIDENT-1 revealed that two patients in the tonapofylline group had had seizures (Ensor & Russell, 2010). Of note, seizures were not reported in studies of oral tonapofylline, and in rat studies, tonapofylline did not cross the blood-brain barrier (Ensor & Russell, 2010). There is insufficient data to determine whether oral formulations of A₁ antagonists are safe or clinically useful.

3.8 Ultrafiltration

Extracorporeal fluid removal has been used for decades in ADHF, typically reserved for patients with fluid overload states that are refractory to diuretics and other medical therapies. Small studies of ultrafiltration in HF have previously demonstrated effective fluid removal, rapid symptom improvement, attenuated neurohormonal activity, and hemodynamic improvements including reduced LV filling pressures and reduced pulmonary arterial pressures without reductions in systemic blood pressure or cardiac index (Marenzi et al., 1993; Rimondini et al., 1987). The landmark UNLOAD (Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure) trial randomized 200 patients with ADHF and volume overload to veno-venous ultrafiltration or intravenous diuretics (Costanzo et al., 2005). Patients in both groups had similar improvements in dyspnea scores, but the patients in the ultrafiltration group had greater weight loss and net fluid loss at 48 hours. Importantly, there were fewer rehospitalizations, rehospitalization days, and unscheduled clinic visits at 90 days in the

ultrafiltration group than in the IV diuretic group. No differences in renal outcomes were seen.

Ultrafiltration can be performed via peripheral or central veins, with rates of fluid removal regulated by a hematocrit sensor and ranging from 10 to 500 mL per hour. Blood flow rates range from 10 to 40 mL per minute, and total extracorporeal blood volume can be as low as 33 mL. Maintenance of a constant hematocrit ensures that the rate of fluid removal from the intravascular compartment is equivalent to the rate of fluid shift from the extravascular to intravascular compartments. Low extracorporeal blood volume and slow fluid removal minimize neurohormonal activation and prevent hypotension. In contrast to the hypotonic fluid removal that occurs with diuresis, ultrafiltration removes isotonic fluid, potentially resulting in greater total sodium removal. The mechanism of the sustained benefit seen in the UNLOAD trial is thought to be related to the attenuation of neurohormonal activity and to the removal of isotonic fluid.

The major limitation to the widespread use of ultrafiltration in HF and the CRS is likely to be the cost of the filters used. In addition, questions remain about patient selection, optimal timing of initiation of therapy, and determination of total fluid volume to be removed. The specific role of ultrafiltration in patients who develop worsening renal function with diuretic therapy is being investigated in CARESS-HF (Cardiorenal Rescue Study in Acute Decompensated Heart Failure), and will help to define the role of this therapy specifically in the CRS population.

3.9 Erythropoietin and correction of anemia

Anemia is common in both HF and CKD, and the term “cardiorenal-anemia syndrome” refers to the coexistence of anemia and the CRS. EPO is widely used in the CKD population to correct anemia to a moderate degree. Studies in this population have shown improved parameters of cardiac performance with EPO therapy, including reduction of left ventricular hypertrophy and dilatation, improved left ventricular ejection fraction, and increased cardiac output (Linde et al., 1996; Low et al., 1989; Low-Friedrich et al., 1991). Studies of EPO and iron administration to patients with HF with or without CKD have shown inconsistent results, but some studies have demonstrated modest improvements in symptoms and functional capacity as well as renal function, ejection fraction, and left ventricular dimensions (Bolger et al., 2006; Palazzuoli et al., 2006; Silverberg et al., 2000; Toblli et al., 2007). The FAIR-HF (Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency) study demonstrated improved symptoms and functional capacity in patients with HF and iron deficiency, even in the absence of overt anemia, treated with intravenous iron as compared to placebo (Anker et al., 2009). The ongoing IRON-HF (Iron Supplementation in Heart Failure Patients With Anemia) and RED-HF (Reduction of Events With Darbepoetin Alfa in Heart Failure) studies will likely further clarify the role of iron and EPO therapies in patients with HF and provide additional insights into the management of the CRS.

4. Conclusions and future directions

The Cardiorenal Syndrome is a pathophysiologic state involving complex feedback processes between the failing heart and failing kidneys, and is associated with a

significantly increased risk of morbidity and mortality compared to either disease process alone. New classification schemes add to our understanding of the processes involved, and help to guide therapy. As the pathophysiology of the CRS becomes better understood, there is potential for the development of novel and rational treatment strategies. Although many promising agents introduced in recent years have produced disappointing results in clinical trials, other strategies, including HSS, ultrafiltration, and low-dose dopamine still hold potential. Larger scale trials of these and other agents are required before their use can be widely adopted. Fortunately, such trials are already underway for ultrafiltration, EPO, and dopamine and the results of these studies are eagerly anticipated. Similarly, established therapies such as β -blockers, ACE inhibitors, and ARBs must be rigorously tested in patients with concomitant cardiac and renal dysfunction to ensure they provide clinical benefit across the spectrum of disease states which characterize the cardiorenal syndrome.

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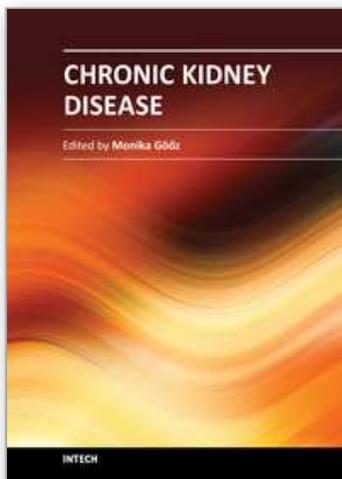
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Chronic kidney disease is an increasing health and economical problem in our world. Obesity and diabetes mellitus, the two most common cause of CKD, are becoming epidemic in our societies. Education on healthy lifestyle and diet is becoming more and more important for reducing the number of type 2 diabetics and patients with hypertension. Education of our patients is also crucial for successful maintenance therapy. There are, however, certain other factors leading to CKD, for instance the genetic predisposition in the case of polycystic kidney disease or type 1 diabetes, where education alone is not enough.

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