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Review Article

Pharmacological Management of Cardiorenal Syndromes

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Cardiorenal syndromes are disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other. The pharmacological management of Cardiorenal syndromes may be complicated by unanticipated or unintended effects of agents targeting one organ on the other. Hence, a thorough understanding of the pathophysiology of these disorders is paramount. The treatment of cardiovascular diseases and risk factors may affect renal function and modify the progression of renal injury. Likewise, management of renal disease and associated complications can influence heart function or influence cardiovascular risk. In this paper, an overview of pharmacological management of acute and chronic Cardiorenal Syndromes is presented, and the need for high-quality future studies in this field is highlighted.

1. Introduction

Cardiorenal syndromes (CRS) affect a broad array of patients in both acute and chronic clinical situations, with significant ramifications in terms of morbidity and mortality. For instance, type 1 CRS, as seen in patients experiencing an abrupt increase in serum creatinine >0.3 mg/dL (>26 μmol/L) during hospitalization for acute decompensated heart failure (ADHF), is associated with increased length of stay, more complications, and higher mortality. In chronic heart failure, the coexistence of chronic kidney disease (CKD) with glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 (type 2 CRS) significantly increases the risk for mortality. Acute kidney injury, for example, following contrast for radiological imaging, has been associated with subsequent adverse cardiovascular events, so-called type 3 CRS. Numerous studies have identified CKD as a graded and independent risk factor for cardiovascular events and outcomes, representing type 4 CRS. Systemic disorders that involve both the heart and kidneys (type 5 CRS) are a heterogeneous group, but when examining sepsis as an example, increasing numbers of organs involved dramatically increases mortality, particularly in those with evidence of septic cardiomyopathy [1] and acute kidney injury [2].

In this paper, we review briefly the pharmacological management of the various subtypes of CRS, highlighting the need for high-quality future studies. Table 1 presents a point-form summary of suggested management for these subtypes, along with pitfalls and questions for future research.

2. Management of Acute Cardiorenal Syndrome (Type 1)

Type 1 CRS appears in the setting of ADHF or cardiogenic shock for a number of reasons, with hemodynamic

Table 1

CRS subtype	General considerations and recommended therapies	Caveats/areas for future investigation
Acute cardio-renal (CRS 1)	Reduce congestion with diuretics, balance negative fluid balance with intravascular refilling	Infusion versus bolus; dose; electrolyte concerns
	Renin-angiotensin blockade may need to be reduced or even withheld with worsening renal function	
	With preserved or elevated blood pressure, empiric use of vasodilators	Limited data from uncontrolled trials; nitroprusside limited by toxicity
	Nesiritide may improve cardiac output and cause significant diuresis	Conflicting results of clinical trials; ongoing trials to determine safety, efficacy, and dose
	With low pressure, poor cardiac output, inotropes may be required as a bridge to recovery or transplantation	Intropes may provoke ischemia or arrhythmia; increased mortality in some studies; mechanical support (balloon pump, ventricular assist device, etc.) may be required
Chronic cardio-renal (CRS 2)	Renin-angiotensin blockade is of primary importance; may need to be reduced or withheld with significantly worsening renal function	Most studies have excluded patients with significant kidney disease; increase in creatinine >30% or potassium >5.0 mmol/L cause for concern
	Aldosterone antagonists may be cautiously considered	Creatinine >2.5 mg/dL (>220 μmol/L) or potassium >5.0 mmol/L were exclusions in clinical trials
	Beta-blockers are important adjuncts in congestive heart failure and/or ischemic heart disease	Some agents (atenolol, nadolol, sotalol) have altered pharmacokinetics; carvedilol may have an advantage over older drugs
	Concomitant anemia may worsen symptoms and outcomes	Unclear role of erythropoiesis-stimulating agents; parenteral iron encouraging in terms of symptoms as well as improved renal function
Acute reno-cardiac (CRS 3)	Contrast nephropathy is a common example of CRS 3; prevention is likely the best strategy	
	Numerous strategies tested; isotonic fluids and possibly N-acetylcysteine have the best evidence to date	Preexisting chronic kidney disease, age, diabetes, and volume contraction are amongst risks that predispose to contrast nephropathy
	Low osmolar, nonionic contrast may reduce risk of CRS 3	
Chronic reno-cardiac (CRS 4)	Multifaceted disorder with both traditional and non-traditional risk factors; graded risk based on degree of chronic kidney disease	Lifestyle modification (smoking, weight control, activity, and nutrition) of probable benefit but limited evidence
	Anemia closely related to poor outcomes; current guidelines recommend starting for sustained hemoglobin <10 g/dL (100 g/L) and targeting 10–12 g/dL (100–120 g/L)	Studies showed increased harm from higher targets; concerns have been raised about stroke risk, and risk in patients with cancer
	Management of chronic kidney disease-related mineral and bone disorders; phosphate binders, vitamin D analogs, controlling PTH	As yet, efficacy largely limited to putative surrogate endpoints; ongoing trials with hard cardiovascular endpoints awaited
	Lipid lowering with statins	Efficacy in dialysis-dependent patients is questioned; in lesser degrees of chronic kidney disease risk reduction is clearly established
Secondary cardio-renal (CRS 5)	Sepsis is a common example of CRS 5; management needs to focus on protecting/optimizing both cardiac and renal function	Other secondary causes of CRS 5 are a fruitful area for ongoing research
	Volume and pressor support to achieve a mean arterial pressure ≥65 mmHg and central venous pressure of 8 to 12 mmHg and adequate oxygen delivery	Early protocol-driven interventions lower risk of adverse renal outcomes and death due to cardiovascular collapse
	Norepinephrine preferred over dopamine in a randomized controlled trial (most patients had septic shock)	Higher incidence of cardiac arrhythmia and trend to increased need for dialysis with dopamine
	Addition of low-dose vasopressin in select patients	May decrease risk of adverse cardiac and renal outcomes

derangements ranging from acute pulmonary edema with hypertension through severe peripheral fluid overload to cardiogenic shock and hypotension [3–5]. Unfortunately, the management of type 1 CRS is largely empiric, as many of the traditional therapies to relieve congestive and/or ischemic symptoms (diuretics, vasodilators, and morphine) [5] have not been subjected to rigorous study. While hypotension and decreased cardiac output with neurohormonal activation have been the traditional explanations for worsening renal function in this setting, recent evidence has implicated high venous pressure and raised intra-abdominal pressure leading to renal venous congestion as important contributors to impairment of kidney function [6, 7], and indeed many patients with ADHF and type 1 CRS have preserved left ventricular ejection fraction and normal or high blood pressure. Hence, strategies to reduce congestion with diuretics and possibly ultrafiltration, and the use of vasodilators in select patients, are important steps in early management.

The goal of diuretic use should be to deplete the extracellular fluid volume at a rate that allows adequate time for intravascular refilling from the interstitium. To achieve adequate diuresis, infusions of loop diuretics have been demonstrated to have greater efficacy than intermittent dosing [8], and certainly loop diuretics are preferred to thiazides, whose actions are diminished in patients with impaired kidney function [9]. In a recent study, ADHF patients who developed hemoconcentration during diuresis (presumed to be diuresed in excess of refilling rate) did in fact have a greater risk of worsening renal function with an odds ratio of 5.3 ($P < .001$), however they also had lower 180-day mortality, with a hazard ratio of 0.31 ($P = .013$) [10]. Diuretics may hence need to be withheld or reduced to allow for plasma refilling. Finding the optimal balance between relief of ADHF symptoms while maintaining adequate kidney function will require further study, and the optimal dose and route of loop diuretic is being studied in the randomized trial DOSE-AHF [11].

If kidney function continues to worsen, blockade of the renin-angiotensin-aldosterone-system (RAAS) may be a contributing factor, necessitating withholding or delaying the introduction of angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) in order to maintain the GFR [12]. As a nonpharmacological strategy to more vigorously manage hypervolemia and circulatory congestion, ultrafiltration was demonstrated in the UNLOAD study to be superior to diuretics, in terms of greater weight loss, less requirement for vasoactive drugs, and fewer rehospitalizations and emergency room visits, with no difference in mortality [13]. The CARRESS-HF trial is currently being undertaken to further define the use of this therapy in patients with type 1 CRS [11].

For type 1 CRS patients with preserved or elevated blood pressure, vasodilators such as nitroglycerin and nitroprusside are often used to relieve symptoms and improve hemodynamics [14], though their efficacy has not been studied through randomized controlled trials, and their effect on reversing or preventing type 1 CRS is unknown. The use of nitroprusside in patients with impaired kidney function is potentially hazardous due to the accumulation of thiocyanate [15], however, in a nonrandomized trial which included patients with varying degrees of kidney function, its use was associated with improved outcomes and stable kidney function [16].

Nesiritide, a recombinant form of human B-type natriuretic peptide, quickly relieves dyspnea in acute heart failure states, through a combination of decreased preload, afterload and pulmonary vascular resistance, and increased cardiac output. It also causes a brisk diuresis due to direct renal effects including afferent arteriolar vasodilation and decreased sodium reabsorption [17]. However, a meta-analysis of trials in patients with ADHF found that nesiritide did not avert type 1 CRS and increased mortality [18]. Ongoing research will hopefully clarify its role in type 1 CRS [19].

When patients have low blood pressure and poor renal perfusion, positive inotropes such as dobutamine or phosphodiesterase inhibitors may be required [5]. However, the use of inotropes may actually accelerate some harmful processes such as ischemia or arrhythmia. Milrinone, for instance, was demonstrated to have a higher incidence of hypotension, more arrhythmias, and no benefit on mortality or hospitalization in ADHF patients [20]. Levosimendan, a phosphodiesterase inhibitor with calcium sensitizing activity, has shown mixed results in terms of the prevention and treatment of type 1 CRS [21, 22]. When patients with ADHF or cardiogenic shock and type 1 CRS are resistant to therapy, more invasive therapies such as intra-aortic balloon pulsation, ventricular assist devices, or artificial hearts may be required as a bridge to recovery of cardiac function or to transplantation.

Finally, a number of classes of agents targeting some of the vasoactive/neurohormonal effector pathways in type 1 CRS, specifically endothelin, adenosine, and vasopressin, have held promise in preclinical and early clinical trials. However, subsequent randomized trials have failed to show a benefit of antagonism of receptors for these targets [23–26].

3. Management of Chronic Cardiorenal Syndrome (Type 2)

Interruption of the RAAS is the primary goal in the management of type 2 CRS. However, RAAS blockade can lead to significant decrease in kidney function, and/or elevated potassium. Studies of RAAS blockade in heart failure have typically excluded CKD patients [27], but it is likely that these agents are renoprotective even in this population. The CONSENSUS trial, for example, included a number of subjects whose serum creatinine increased by 30% or greater with enalapril [28]. However, creatinine tended to stabilize and in many instances improved over the course of the study. Typically it is recommended that RAAS blockade may be carefully titrated provided the serum creatinine does not continue to rise beyond 30% and potassium is consistently below 5.0 mmol/L.

In terms of aldosterone blockade, drugs such as spironolactone and eplerenone are an important adjunct to therapy in patients with severe heart failure [29, 30]. However, the use of these agents in patients with CKD, and particularly in combination with other RAAS blockade, can dramatically

increase the risk of hospitalizations and mortality secondary to hyperkalemia [31]. Excluding patients with moderate CKD (creatinine level $\geq$2.5 mg/dL or 220 μmol/L) or hyperkalemia >5.0 mmol/L, which were exclusion criteria in the Randomized Aldactone Evaluation Study (RALES) [29], will minimize potential life-threatening complications [32].

Interruption of sympathetic tone through the use of beta-blockers is another important strategy for patients with congestive heart failure or ischemic heart disease. In general, these drugs should not adversely affect kidney function. Certain beta-blockers may be relatively contraindicated in CKD because of altered pharmacokinetics, such as atenolol, nadolol, or sotalol [33], and it is wise to consult a pharmacopoeia when prescribing beta-blockers to patients with CKD. Carvedilol, a beta-blocker with α_1 blocking effects, has been demonstrated to have favourable effects on kidney function in some CRS patients, hence may have a benefit over older beta-blockers [34].

Both congestive heart failure and CKD are associated with anemia, the latter of which is commonly treated with erythropoiesis-stimulating agents. Furthermore, the action of erythropoietin in the heart may reduce apoptosis, fibrosis, and inflammation [35, 36]. Hence, there has been intense interest in using erythropoiesis-stimulating agents in heart failure patients [37]. A small controlled trial suggested that administration of erythropoiesis-stimulating agents in patients with type 2 CRS and anemia led to improved cardiac function, reduction in left ventricular size, and lowering of BNP [38]. However, more recent work did not find significant improvement in a variety of important clinical parameters [39]. Ongoing clinical trials are required to establish if erythropoiesis-stimulating agents have a role to play in the management of congestive heart failure and type 2 CRS. Another approach to anemia management in type 2 CRS is parenteral iron. In the FAIR-HF study, patients were randomized to ferric carboxymaltose or placebo, and the active treatment group experienced an improvement in heart failure symptoms, Patient Global Assessment, 6-minute walk test and quality of life [40]. They also experienced a higher GFR at the study conclusion of 3.8 mL/min/1.73 m^2.

4. Management of Acute Reno-Cardiac Syndrome (Type 3)

In type 3 CRS, acute kidney injury occurs as a primary event (e.g., acute glomerulonephritis) or secondary event (e.g., radiocontrast, exogenous or endogenous nephrotoxins, postsurgical, etc.), and cardiac dysfunction is a common and often times fatal sequela [41]. A common example of type 3 CRS occurring in the hospital setting is contrast nephropathy, particularly in patients undergoing coronary and other angiographic procedures who have risk factors such as preexisting CKD, diabetes, older age or volume contraction. In these susceptible populations, prevention may provide the best opportunity to "treat" or avoid type 3 CRS. Many potential preventive strategies have been studied, including parenteral hydration (hypotonic or isotonic saline or bicarbonate), diuretics, mannitol, natriuretic peptides, dopamine, fenoldopam, theophylline, and N-acetylcysteine [42, 43]. To date, isotonic fluids have been the most successful intervention, with some controversy surrounding the effectiveness of N-acetylcysteine. Using a sensitive definition of acute kidney injury, Solomon and colleagues identified a possible role for the low-osmolar, nonionic monomer iopamidol in the prevention of contrast nephropathy [44]. In addition, they identified that the research subjects who experienced acute kidney injury were almost twice as likely to have major cardiovascular events (death, stroke, myocardial infarction, or dialysis) during the follow-up period, indicative of the seriousness of type 3 CRS.

Treatment of primary kidney diseases such as acute glomerulonephritis or kidney allograft rejection may potentially lessen the risk of type 3 CRS, but this has not been systematically studied. Furthermore, many immunosuppressive drugs used for such treatment have adverse effects on the cardiovascular system through their effects on blood pressure, lipids, and glucose metabolism. For instance, a recent meta-analysis comparing the calcineurin-inhibitors cyclosporine and tacrolimus found greater dyslipidemia in the cyclosporine group and higher risk of new onset diabetes in the tacrolimus group [45]. The drug sirolimus, working through the mammalian target of rapamycin (mTOR) pathway, leads to even greater perturbations in lipids and higher requirement for lipid-lowering therapy [46]. While direct and indirect influences of these agents may be potentially harmful to the heart, some investigators have implicated calcineurin in the development of left ventricular hypertrophy and heart failure in animal models [47]. The role of immunosuppression in the prevention or conversely the development of type 3 CRS needs further study.

5. Management of Chronic Reno-Cardiac Syndrome (Type 4)

The management of type 4 CRS is a multifaceted approach focusing on the reduction of cardiovascular risk factors and complications common to CKD patients. These include, but are not limited to, anemia, hypertension, altered bone, and mineral metabolism, dyslipidemia, smoking, albuminuria and malnutrition [48, 49]. Several therapies targeting such uremic complications as anemia, homocysteine, calcium-phosphate product and hyperparathyroidism are supported by observational studies demonstrating the association between adverse cardiovascular events and these conditions.

In observational studies, the treatment of anemia seems to lessen cardiovascular events, however this has not been borne out in randomized trials where higher hemoglobin targets have been associated with worse outcomes [50–53]. Hence, the use of erythropoiesis-stimulating agents to prevent type 4 CRS seems to be ineffective.

Elevated homocysteine has been associated with worsening cardiovascular outcomes in a number of observational studies [54], and has been a target of study in CKD. However, vitamin therapy to lower homocysteine has been unhelpful in patients with advanced CKD [55, 56] and harmful in patients with diabetes and more moderate CKD [57].

Observational studies have implicated elevated calcium-phosphate product, elevated phosphate, elevated parathyroid

hormone, and inadequate vitamin D receptor activation as potential risk factors for type 4 CRS [58–60]. Clinical trials to date have been generally disappointing. A meta-analysis of trials studying the use of the phosphate binder sevelamer indicated no significant benefit of therapy [61]. However, a subgroup analysis in older patients at higher cardiovascular risk suggests that phosphate binding may improve outcomes [62] and intensive lowering of calcium-phosphate product improves levels of C-reactive protein [63]. With respect to parathyroid hormone, high levels have been associated with adverse cardiovascular outcomes in CKD [59], and a systematic review revealed that cinacalcet, a drug used to lower parathyroid hormone, decreased hospitalizations related to cardiovascular disease [64]. A large randomized trial of cinacalcet is examining hard cardiovascular endpoints and mortality [65], and trials of phosphate binders and vitamin D analogs are ongoing.

The use of "statins" (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) is a cornerstone of risk factor modification in patients at risk for cardiac disease. Unfortunately, two high-profile negative trials in dialysis patients [66, 67] have cast a shadow of doubt over the use of statins to prevent type 4 CRS, at least in advanced CKD patients. The recently published Study of Heart and Renal Protection (SHARP) included 3,023 dialysis patients and 6,247 CKD patients not on dialysis, and preliminary results showed that a combination of simvastatin and ezetimibe lowered the risk of major atherosclerotic events, with a risk ratio of 0.83 (0.74–0.94, $P = .0022$) [68]. Of interest, the subgroup of patients on dialysis seemed to experience less of a benefit from the drug therapy, and all-cause mortality was unaffected. The full publication is eagerly awaited. In an earlier meta-analysis [69] Strippoli et al. demonstrated significant reductions in cardiovascular end points in CKD patients treated with statins, though again all-cause mortality was unchanged. Statins did not, however, cause adverse events in subjects with CKD compared to those with normal kidney function, and the SHARP study indicated that the combination of simvastatin and ezetimibe in this population was well tolerated with no hepatoxic or myopathic complications.

6. Management of Secondary Cardiorenal Syndrome (Type 5)

Examples of type 5 CRS include a heterogeneous group of disorders, such as sepsis, systemic lupus erythematosus, amyloidosis, and diabetes mellitus [70]. It is difficult to formulate a treatment strategy to encompass all of these disorders, but more important is the recognition that injury to one organ is likely to influence or injure the other organ, and *vice versa*. Therapies directed to the improvement in function of one organ need to consider the interaction with, and role of, the other.

As sepsis is one of the more common acute disorders that involves multiple organs, and often causes codysfunction of kidneys and heart, it provides a suitable example for the discussion of type 5 CRS and its management. The study of early goal-directed therapy by Rivers et al. demonstrated that early intervention significantly decreased in-hospital death due to cardiovascular collapse by approximately half (21.0 versus 10.3%; $P = .02$), and another study of protocol-driven targets in patients with septic shock [71] showed a significant reduction in the incidence of acute renal failure from 55.2% to 38.9% ($P = .015$). De Backer and colleagues compared dopamine with norepinephrine in the management of shock (the majority with septic shock) and found that the dopamine group had a higher incidence of cardiac arrhythmia, while displaying a trend towards greater dependence on renal replacement therapy [72]. Additionally, an important randomized study of conservative versus liberal fluid resuscitation in patients with acute lung injury [73] found that the more conservative strategy improved not only outcomes related to lung injury itself, such as oxygenation and ventilator days, but this strategy also led to less cardiovascular failure and a trend towards improved renal outcomes. Intriguingly, animal studies indicate that in spite of increased coronary and renal blood flow, these organs demonstrate diminished function in sepsis [74]. Another study indicated that low-dose vasopressin was effective in limiting cardiac and kidney injury in sepsis [75]. Recognition of type 5 CRS as an entity in sepsis and other systemic disorders will allow further research into the signalling and mechanisms of injury and allow for the development of rational and effective therapies.

7. Conclusions

The subtypes of CRS discussed in this paper present unique management challenges, but also opportunities for further research. Sadly, many pivotal heart failure trials of the past decades which have been instrumental in guiding therapy for millions of patients worldwide have systematically excluded patients with acute or chronic kidney disease, making it difficult to provide evidence-based treatment guidelines for type 1 and 2 CRS. The recognition of acute kidney injury as an important clinical outcome, coupled with more stringent and standardized diagnostic criteria, has led to a tremendous increase in research activity in recent years. The increased understanding of downstream consequences of acute kidney injury, and in particular its role in type 3 CRS, has only recently been appreciated. Clearly more high-quality research in this area is necessary. Finally, an astonishing number of cardioprotective trials in type 4 CRS have been negative [76]. This underscores the need to recognize CKD as a factor that not only heightens risk of cardiovascular disease, but also modifies (or even negates) the effect of treatments proven effective in other populations. Understanding the complex bidirectional interactions between the heart and the kidneys can only help foster future drug development and investigations into the prevention and management of all subtypes of CRS.

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