The native natriuretic peptides and their respective cGMP-linked receptors possess renal-enhancing actions but are limited by untoward effects on the kidney. Novel drug discovery and design taking key parts of native natriuretic peptides and creating designer drugs like CD-NP may optimize renal-favorable effects such as renal protection and limit adverse actions such as excessive hypotension but still unload the heart. Second, use of genomic research tools may provide opportunities to find novel natriuretic peptides resulting in the engineering of renal-specific peptides such as AS-BNP1, which may prove efficacious in the cardiorenal syndrome. We all await exciting results of new and ongoing trials of these novel natriuretic peptides for cardiorenal disease.

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References
1. Coresh J, Astor B, Sarnak MJ. Evidentiary approaches is directed at controlling atherosclerotic comorbidities, while improving the general comorbidity and associated clinical condition. In CKD stages 1–3, the goal of therapy is to improve the general condition of the patient.

Atherosclerosis
To reduce the impact of the cardiorenal syndrome on CVD morbidity and mortality, the following therapeutic strategies are currently recommended:

- blood pressure (BP) control
- albuminuria reduction
- dyslipidemia and statin therapy
- antiplatelet agents
- vitamin D–calcium–phosphorus control

Blood pressure control
Long-term cardiorenal protection involves two important concepts: BP control to a much lower target of systolic BP < 130 mmHg and use of an agent that blocks the renin-angiotensin-aldosterone (RAAS) system as base therapy. However, appropriate BP control becomes more difficult as kidney function declines. In addition, patient with CKD also have increased rates of uncontrolled hypertension.

Antihypertensive therapy should be initiated with an angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB). The antihypertensive regimen can be further modified according to BP-lowering efficacy and CVD reduction. Coadministration of diuretics is mandatory: thiazides in early/mild stages and loop diuretics when serum creatinine > 2.5 mg/dL. Potassium-sparing diuretics are contraindicated. Addition of beta blockers affords cardio-protective benefits such as angina reduction, improved left ventricular function, reduced rates of hospitalization and readmission, and reduced rates of sudden death in patients after myocardial infarction and in those with concurrent heart failure.

The current consensus is to lower SBP to at least 130 mmHg. However, further reduction may be unsafe, particularly in high risk patients as it has been associated with increased CVD risk.

Albuminuria
Reduction of albuminuria, a treatment target associated with improved cardiovascular and renal outcomes, can be achieved by BP reduction with RAAS blockade. However, in a substantial number of patients, albuminuria > 1 g/day persists despite SBP < 130 mmHg and continued RAAS blockade. This condition results from secondary increase in aldosterone production and responds to addition of spironolactone or eplerenone on top of RAAS blockade.

Dyslipidemia and statin therapy
Patients with CKD and ESRD exhibit a pattern of mixed dyslipidemia characterized by decreased high density lipoprotein cholesterol (HDL-C), increased triglycerides, and increased low-density lipoprotein cholesterol (LDL-C). The National Kidney Foundation’s (NKF) recommended target goals for treating dyslipidemia in patients with CKD are: total cholesterol < 200 mg/dL, LDL-C < 100 mg/dL, HDL-C ≥ 40 mg/dL.

NKF recommends lifestyle changes in accordance with pharmacotherapy. Based on the lipid pattern of dyslipidemia most commonly found in CKD, with elevated triglycerides and low HDL-C, treatment with nicotinic acid and fibrate is indicated. However, fibrate use in patients with ESRD has been linked to rhabdomyolysis, possibly generating additional acute renal failure.

For reduction in LDL-C, statins are first-line agents. These drugs are well tolerated and safe. They have been shown to reduce cardiovascular events and mortality in CKD patients, and to attenuate declines in renal function and increase in albuminuria. Although considered safe for use in CKD, dose reduction is required.

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**Cardiorenal Syndrome**

**Clinical Presentation**

- Atherosclerosis (CKD stages I—II)
- Cardiomyopathy (CKD stages IV—V, ESRD)
- CAD/MI
- Stroke
- PVD
- Hypertension control
- Albuminuria reduction
- Dyslipidemia/statin therapy
- Antiplatelets
- Vitamin D—calcium—phosphorus metabolism

**Therapy**

- Beta blockers
- RAAS blockade
- Diuretics
- RRT/ultrafiltration
- Vasopressin antagonists
- ESA

**Diuretics**

- Furosemide
- Hydrochlorothiazide
- Spironolactone
- Indapamide

**Vasodilator therapy**

- Nitroglycerin
- Nesiritide

**Renal replacement therapy (RRT)/ultrafiltration**

- Hemodialysis
- Peritoneal dialysis
- Continuous renal replacement therapy

**Abbreviations:** RRT, renal replacement therapy; PVD, peripheral vascular disease; ESA, erythropoiesis-stimulating agents

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**Cardiomyopathy**

Chronic heart failure (CHF) occurs in about 25 percent of patients with ESRD and accounts for 50 percent of cardiovascular disease (CVD) mortality. In ESRD, CHF results from a uremia-specific type of cardiomyopathy. Its prevalence increases with further deterioration of renal function and may progress to an ominous state of acute decompensated heart failure (ADHF).

The heterogeneous and complex pathophysiology of cardiorenal dysfunction in these patients makes management an intricate clinical challenge. To date, there is no single therapeutic approach guaranteed to succeed, because of the unique risk profile and combination of co-morbidities in each patient.

**General measures**

The patient needs continuous hemodynamic monitoring, especially if BP is low and the filling pressure uncertain. Body weight, the single most important indicator, should be recorded frequently.
the treatment of fluid overload have been explored, including the use of mechanical means. The most notable development in this respect has been veno-venous ultrafiltration. In contrast to diuretics that produce hypotonic urine and intravascular volume contraction, leading to further sodium and water retention, ultrafiltration results in the removal of isotonic fluid without causing neurohormonal activation or disturbances in serum electrolytes (Figure 2). In the Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure (UNLOAD) study ultrafiltration achieved greater fluid and weight loss than intravenous diuretics, reduced 90-day rehospitalization and unscheduled visits, and appeared to be an effective alternative therapy. The effect of ultrafiltration on mortality, however, remains to be established.

**Renin Angiotensin Aldosterone (RAAS) blockade**

Owing to extensive and multiple detrimental effects of chronic RAAS activation, RAAS inhibition has emerged as a mainstay of treatment for patients with heart failure. Angiotensin converting enzyme (ACE) inhibitors improve symptoms of heart failure and reduce morbidity and mortality. Despite a mild reduction in GFR due to blunting of angiotensin II-induced vasoconstriction of the efferent arterioles, ACE inhibitors preserve renal function long-term. However ACE inhibitors should be used cautiously, starting with small doses, in patients with renal insufficiency in order to prevent marked deterioration in renal function.

An alternative mechanism of blocking the effects of angiotensin II is with ARBs, either in place of or in addition to ACE inhibitors. Both of these strategies have been reported to benefit patients with heart failure.

Although both ACE inhibitors and ARBs reduce aldosterone production, further aldosterone inhibition with specificaldosterone antagonists provides additional benefits. They block renal sodium and water reabsorption, reduce fibrosis in the kidney and in the heart helping to preserve cardio renal function, and reduce significantly mortality in advanced heart failure. However, they should be used cautiously in patients with significant renal dysfunction to prevent hyperkalemia.

Aliskiren, a direct renin inhibitor, has been shown to reduce BNP levels. Urinary aldosterone in heart failure patients already on ARBs and ACE inhibitors (Aliskiren Observation of Heart Failure Treatment [ALOFT]) may be considered a therapeutic option in such patients.

**Inotropes**

A trial of inotropic therapy using dopamine or milrinone may be considered in renal impaired patients with low cardiac output. However, the use of inotropes in these patients has not been associated with improved survival.