Renal dysfunction in heart failure patients or the presence of cardiac functional impairment in renal failure patients invariably means a worsening prognosis in either setting (1–7). Clinical and experimental studies have concluded that there is not one unique mechanism for cardiorenal syndrome. Decreased renal perfusion in the heart failure setting has been associated with renal hypoxia, increased sympathetic activity, elevated central venous pressure and increased intra-abdominal pressure, oxidative stress, endothelial dysfunction, as well as with activated renin-angiotensin-aldosterone system (RAAS) and vasopressin system (REF) (8–13).

Beyond elucidating the mechanisms of this syndrome, there is an unmet need for innovative therapeutics that aim both at the heart and the kidney to enhance both organ systems in the control of optimal cardiac function. Indeed, the goal of a cardiorenal therapeutic should be to 1) unload the heart including decrease venous pressure while minimizing reductions in blood pressure, 2) directly target the nephron to preserve or enhance glomerular filtration rate (GFR) and reduce salt and water retention, and 3) suppress activated RAAS and arginine vasopressin (AVP) systems.

The cardiac natriuretic peptides are a family of hormones that include atrial natriuretic peptide (ANP), b-type or brain natriuretic peptide (BNP), and c-type natriuretic peptide (CNP). These peptides act via their second messenger cGMP. There are two receptors, GC_A (guanylate cyclase A receptor, GC-A) and GC_B (guanylate cyclase B receptor, GC-B) that bind to BNP. The peptides have multiple actions. They are natriuretic (via GC_A), renin and aldosterone inhibiting (via GC_A), venodilating (GC_A), anti-fibrotic (GC_A), anti-hypertrophic (GC_A), lusitropic (GC_A), anti-apoptotic (GC_A), and vascular regenerating (GC_A) (14–16).

Among this family of peptides, the only approved for therapeutic use in the United States is BNP (neuropeptide), specifically in the setting of acute decompensated heart failure (ADHF). BNP is a GC-A receptor agonist with potent arterial vasodilating properties. It enhances renal function in conditions such as cardiopulmonary bypass surgery, but in ADHF and because of excessive hypotension it may impair renal function. It is hoped that the resulting controversy will be clarified soon by completion of the ASCEND-HF trial in patients with ADHF, which will address the safety and efficacy of neuropeptide in 7000 individuals randomized to BNP or standard care (17).

The aim of improving natriuretic peptide therapy in terms of safety and efficacy led to the design of a novel chimeric natriuretic peptide that unloads the heart but does not cause excessive hypotension while enhancing renal function. This peptide, CD-NP, is currently being tested in phase II trials. CD-NP is a designer NP that integrates mature CNP with the C-terminus of DNP (18–20). The rationale for the design of CD-NP is based on the vascular actions of CNP produced by the endothelium and acting through GC-B, which possesses venodilatory properties causing less hypotension than ANP (19). CNP also accelerates endothelial repair and is potentially anti-fibrotic. It inhibits hypertrophy in cardiomyocytes but is not natriuretic nor does it suppress the RAAS (21). CNP lacks a C-terminus, making it very susceptible to degradation by neutral endopeptidase (NEP), the enzyme that degrades natriuretic peptides. DNP, on the other hand, is a natriuretic peptide that was originally found in a snake, the Dendroaspis angusticeps (Eastern Green Mamba) (22). This peptide binds to the GC-A receptor, the same receptor that ANP and BNP bind to, giving it natriuretic and diuretic properties. Importantly, the 15-amino acid C-terminus confers high resistance to degradation. CD-NP therefore is a designer chimeric natriuretic peptide, the first of its kind, that represents a dual GC-A and GC-B receptor agonist (18,19). Thus, CD-NP was engineered to exploit the characteristics of CNP so that CD-NP would be less hypotensive than BNP and possess renal, cardiac preload reducing, and RAAS-suppressing actions.

Preclinical studies in the laboratory showed that in plasma and urine, CD-NP compared to CNP had enhanced cGMP generation (18). In a different preclinical study, comparison to BNP showed that CD-NP had less hypotensive effects than BNP and that it possessed GFR enhancing properties (18,19). Moreover, CD-NP reduced cardiac filling pressures and suppressed renin. In healthy individuals, CD-NP increased cGMP production in plasma as well as in urine compared to placebo. It also increased urinary sodium excretion without excessive hypotension, and it decreased aldosterone plasma levels. In preliminary studies in patients with heart failure, CD-NP improved GFR estimated from creatinine clearance, reduced cardiac filling pressures as demonstrated by a reduction in plasma, and suppressed aldosterone (19).

Recently, a second designer natriuretic peptide based on a genomic approach has been reported (23,24). In this case, based upon alternative splicing of the BNP gene, a BNP-like peptide was discovered and has been called AS-BNP. Owing to intron retention, alternative splicing codes for a unique 34-amino acid C-terminus while preserving the remainder of native BNP. From AS-BNP, a novel shorter amino acid peptide was designed that results in a renal-selective action. In experimental heart failure, this designer peptide (AS-BNP1) enhances GFR, increases sodium excretion, and suppresses renin. Importantly, it has no effect on blood pressure, which is preserved (25). It is hypothesized that this second designer peptide may activate a novel renal natriuretic peptide receptor. Clinical trials are expected to start soon.

The cardiorenal syndrome will continue to be a clinical challenge. We still need to understand its mechanisms and seek more effective and safe therapies.
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-BNP, 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.

By Adel Berbari, MD

Treatment Options in Cardiorenal Syndrome

By Adel Berbari, MD

Interaction between chronic kidney disease (CKD) and cardiovascular disease (CVD), termed the cardiorenal syndrome (CRS), is characterized by enhanced risk of atherosclerosis and uremia-related myocardial disorders (Figure 1). While milder degrees of renal impairment (CKD stages 1–3) are associated with accelerated risk of atherosclerosis and uremia-related myocardial disorders (CKD stages 1–3) are associated with increased cardiovascular disease and mortality in a community-based cohort with mild renal insufficiency, the more severe and advanced stages of renal dysfunction and end stage renal disease (ESRD) (stages 4, 5, and ESRD) (Figure 1).

Therapeutic options in CRS depend on the severity of the degree of renal impairment and associated clinical conditions. In CKD stages 1–3, the goal of therapeutic approaches is directed at controlling atherosclerotic comorbidities, while in CKD 4, 5, and ESRD, the aim 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

Low-normal 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 offers cardio-protective benefits such as angina reduction, improved left ventricular function, reduced rates of hospitalization 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 mm Hg. 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 recommended.

Continued on page 20