Significant progress has been made in the understanding of the neurohormonal factors that contribute to the progression of chronic renal and cardiac failure and the development of target-organ damage in patients with hypertension and diabetes.\(^1\-^3\) We herein review some of these advances, including a new therapeutic strategy for potentially enhancing cardiorenal protection in patients with these disorders.

In addition to suffering the consequences of chronic organ failure, the kidneys and heart produce chemicals that mediate pathophysiological changes in vascular tone, salt and water balance, cellular hypertrophy, and fibrosis underlying these disease processes. The kidneys produce renin in the juxtaglomerular cells of the macula densa, which activates the renin-angiotensin-aldosterone system (RAAS), and the heart synthesizes the components of the natriuretic peptide system (NPS). The RAAS and NPS act as counterregulators in renal and cardiovascular homeostasis, producing opposing effects throughout the evolution of disease (Figure 1). These systems also act indirectly through their influence on neurohormones such as the sympathetic amines, arginine vasopressin, endothelin-1, and adrenomedullin.\(^4\,^5\) Besides these 2 endocrine systems, the kidney also possesses a paracrine RAAS and NPS that modulate sodium and water transport and urodilatin metabolism.\(^6\)

In hypertension, chronic renal disease, and heart failure, the RAAS produces increased levels of the octapeptide angiotensin II (Ang II), which affects vasomotor tone and renal function and ultimately leads to vasoconstriction and intravascular volume expansion.\(^7\) Angiotensin II also produces differential contractions of the afferent and efferent glomerular arterioles and mesangial cells, thus increasing glomerular filtration pressure,\(^8\) and causes sodium and water reabsorption directly in the proximal tubules and indirectly in the collecting ducts by triggering release of aldosterone.\(^9\,^10\)

The RAAS modulates its own activity by stimulating expression of counterregulatory factors such as the peptides of the NPS and adrenomedullin.\(^11\) Finally, Ang II and aldosterone contribute to chronic cardiorenal damage by promoting glomerular hypertrophy and mesangial and tubular interstitial fibrosis and by inducing myocardial hypertrophy and fibrosis (cardiac remodeling).\(^12\,^16\) In diabetes, Ang II may act synergistically with hyperglycemia to promote hyperfiltration and proteinuria, leading to diabetic nephropathy,\(^17\) whereas in the heart it may promote insulin resistance, participating in the systolic and diastolic dysfunction characteristic of diabetic cardiomyopathy.\(^2\)

Angiotensin II is released from its precursor, the decapeptide angiotensin I, through the actions of the protease angiotensin-converting enzyme (ACE). The ACE contributes further to vasoconstriction and volume expansion by degrading bradykinin, a potent vasodilator and natriuretic and antifibrotic peptide, which is highly expressed in vascular and renal cells.\(^18\,^21\)

Angiotensin-converting enzyme inhibitors have been demonstrated to be effective in the management of hypertension and heart failure, especially in patients with diabetes and renal impairment.\(^2\,^17\,^22\) Generally, an average of 3 antihypertensive agents are required to adequately control blood pressure (BP) in patients with diabetes, and this contributes to the inad-
The NPS is a cardiovascular endocrine system consisting of the following 3 peptides with vasodilating, natriuretic, diuretic, lusitropic, and antiproliferative/antifibrotic properties: atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP). These peptides counterregulate many of the pathophysiological influences of the RAAS.21

Atrial natriuretic peptide is synthesized in storage granules within atrial cardiomyocytes and is released in response to atrial distention. In addition, ANP expression may be stimulated directly by Ang II, endothelin-1, or adrenomedullin.2,10 Atrial natriuretic peptide reduces intravascular volume and pressure by means of arterial and venous dilation and enhancement of renal excretion of sodium, chloride, and water.1,2 It also attenuates production of renin, Ang II, and Ang II–stimulated aldosterone release and inhibits sympathetic nervous system activity.24

Brain natriuretic peptide, although originally isolated from the porcine brain, is synthesized primarily in ventricular cardiomyocytes in response to ventricular pressure or volume stress. Its physiological effects are similar to those of ANP, and it becomes the major circulating natriuretic peptide during long-term volume expansion in chronic cardiorenal disease.

C-type natriuretic peptide, also isolated from porcine brain, is synthesized in vascular endothelium in response to shear stress, and in addition by circulating ANP or BNP. Unlike ANP and BNP, which exert their action in the systemic circulation, CNP acts locally in a paracrine manner, as a vasodilator and a potent inhibitor of vascular and glomerular proliferation and interstitial matrix production.39,40

The natriuretic peptides elicit cellular responses through activation of the following 2 cell surface receptor proteins (NPRs) that have unique extracellular binding domains: NPR-A and NPR-B. The first receptor, NPR-A, selectively binds ANP and BNP, leading to the peptides’ similar physiological responses. The next receptor, NPR-B, recognizes and binds CNP, resulting in vasodilatory and antiproliferative activities. Both of these receptors contain cytoplasmic guanylate cyclase domains, which catalyze the formation of cyclic guanosine monophosphate (cGMP) upon ligand binding. Cyclic GMP acts as a second messenger, responsible for a cell’s physiological responses to natriuretic peptide stimulation. Physiological responses to natriuretic peptides are therefore determined largely by the location and density of NPRs in target tissues (eg, kidneys, blood vessels, and heart). A third receptor for natriuretic peptides, NPR-C, is the most prevalent of the 3 receptors and binds all 3 natriuretic peptides. It internalizes natriuretic peptides and is responsible for clearance of about half of circulating natriuretic peptides, with the remaining half degraded enzymatically by neutral endopeptidase (NEP).

Neutral endopeptidase is widely expressed throughout the body and is found in high concentrations in the brush border of renal tubules and in the lungs, intestines, adrenals, brain, and heart. Neutral endopeptidase is a zinc-containing cell surface protease with structural simi-
latories to ACE. It also has enzymatic activity against other important vasoreactive peptides, including the dilators bradykinin and adrenomedullin and the constrictors endothelin-1 and Ang II. Inhibition of NEP can therefore result in physiologically relevant elevations in circulating natriuretic and vasoactive substance levels.

The normal renal effects of NPS activity have been determined from a number of experimental studies of ANP. Maack et al administered ANP to anesthetized dogs and found decreases in mean BP, plasma renin activity, and plasma aldosterone levels and increases in glomerular filtration rate (GFR); clearance of water, sodium, and potassium; and effective renal plasma flow. Marin-Grez et al examined ANP in a rat model and discovered that the peptide increases GFR by dilating afferent and constricting efferent glomerular arterioles, thereby increasing glomerular hydraulic pressure. Roy showed that ANP also increases distal sodium delivery by inhibiting sodium reabsorption in the proximal renal tubules, although Harris et al subsequently determined this to be caused indirectly by ANP inhibition of Ang II–mediated sodium transport. Sonnenberg et al demonstrated that ANP directly inhibits sodium transport in the collecting ducts. Zhou and Fiscus found that ANP and BNP promote renal arterial vasodilation by relaxing vascular smooth muscle in rings of renal arteries isolated from rats.

**THE NPS IN CARDIORENAL DISEASE**

The effects of the NPS have been investigated in a variety of animal models of cardiorenal disease. In a dog model, Akabane et al produced elevated BP and marked declines in GFR, renal plasma flow, urine volume, and sodium excretion through prolonged, unilateral renal artery occlusion. The investigators then delivered postocclusion intrarenal artery infusions of ANP and significantly reversed the abnormal variables. Similarly, Conger et al found that ANP reduced serum creatinine levels, increased GFR and effective renal plasma flow, and protected tubular morphology in a rat model of established ischemic renal failure produced by intra-renal norepinephrine.

Natriuretic peptides exhibit powerful antiproliferative and antifibrotic activity, protecting against end-organ damage in chronic cardiorenal disease. Even in response to such strong mitogenic signals as Ang II and transforming growth factor β, ANP and BNP can reduce vascular smooth cell proliferation. Gene expression of NPR-A, but not NPR-B or NPR-C, is significantly elevated in the glomeruli of spontaneously hypertensive rats. Transgenic mice expressing high levels of ANP have been found to be consistently hypertensive, whereas salt-sensitive hypertension developed in mice made genetically deficient in ANP. In an experiment using Dahl salt-sensitive hypertensive rats, Lin et al transfected the human ANP gene within an adenoviral vector and found that the gene therapy significantly lowered BP and enhanced GFR, renal plasma flow, and sodium and water excretion. End-organ damage was diminished with significant attenuation of glomerulosclerotic lesions, tubular injury, arterial thickening, and cardiac hypertrophy. Suganami et al found that overexpression of BNP ameliorates glomerular injury in subtotal nephrectomized mice and protects against mesangial expansion and proliferation in immunemediated renal injury. Likewise, CNP has been demonstrated to reduce mesangial cell proliferation and matrix accumulation in rat glomeruli, and also to protect against vascular smooth muscle cell proliferation in response to balloon injury in the rat carotid artery. Similar findings have been reported for the transgenic expression of adrenomedullin in the Goldblatt hypertensive and in the Dahl salt-sensitive rat, with attenuation of BP, glomerular sclerosis, tubular disruption, and protein casts. These data suggest that the natriuretic peptides might have a therapeutic role in controlling the hyperplastic and hypertrophic responses underlying disease progression in various chronic cardiorenal disorders, in addition to their physiological role in moderating normal cellular growth and repair processes.

Diabetes is the most commonly reported cause of chronic renal failure, and the involvement of the NPS has been examined in experimental diabetes. Geiger et al found that in rats with streptozotocin-induced diabetes, although GFR and BP were significantly increased, plasma ANP levels remained normal. However, when concomitant chronic renal disease was simulated by subtotal nephrectomy, ANP levels became elevated. Blood pressure increases became marked and proteinuria became prominent, accompanied by severe histological changes that included mesangial expansion and nodular glomerulosclerosis. Hirata et al found ANP levels to be moderately increased in streptozotocin-induced diabetic rats. Increasing plasma ANP levels further by raising atrial pressure with albumin infusion or directly by administering exogenous ANP increased sodium excretion and proteinuria, which are effects that could be reduced by ANP receptor antagonists. These authors suggested that diabetic hyperglycemia stimulates ANP secretion osmotically through induced right atrial fluid overload and that elevated ANP levels increase intraglomerular capillary pressure, contributing to hyperfiltration and proteinuria. Vesely et al also found ANP levels to be increased in spontaneously diabetic rats owing to a combination of increased blood volume stimulation and decreased clearance due to diminished renal function.

**THE NPS IN HEALTHY SUBJECTS**

Cuneo et al tested the responses of healthy human subjects being given high- and low-salt diets to exogenously administered ANP at levels ordinarily found in circulating disorders. They reported a 3-fold increase in sodium excretion (reduced by 11% by a low-salt diet) and a 2-fold increase in urine volume. All components of the RAAS were inhibited, regardless of dietary salt intake, with decreased plasma renin activity and Ang II and aldosterone levels that reflected the direct effects of ANP on renin and aldosterone secretion. Blood pressure did
not change, supported by a reflex increase in plasma norepinephrine. Plasma levels of vasopressin were also not affected. Lack of a BP response to ANP in healthy subjects was also observed in another study.63

Although ANP reduces renin and aldosterone responses in experimental conditions, this has not been observed in human studies, in which no changes in the levels of plasma renin, Ang II, or aldosterone were observed.62,63 This likely reflects the reflex activation of the sympathorenal system in response to the vasodilation induced by ANP.1,62,63 Nevertheless, GFR and urinary water, sodium, and chloride excretion were markedly enhanced.63 On the other end of the spectrum, Solomon et al64 administered very low levels of ANP to healthy subjects and found no change in BP or GFR, despite significant diuresis and natriuresis, probably related to ANP effects on distal tubular transport or collecting duct water and sodium transport. The combined evidence shows a consistent natriuretic and diuretic response to ANP in healthy subjects, with dose-dependent BP reductions related to normal homeostatic reflexes.

Although the effects of BNP are generally similar to those of ANP, physiological differences have been observed in healthy subjects. Hunt et al65 administered equimolar ANP and BNP infusions and found that although both peptides produced comparable natriuresis, plasma volume contraction, and plasma aldosterone inhibition, cGMP plasma levels were 4-fold greater with ANP. However, ANP had greater potency in inhibiting the aldosterone response to Ang II. Another group reported BNP to be severalfold more potent than ANP in its vasodepressor, diuretic, and natriuretic properties, but found RAAS inhibition by both peptides to be comparable.66 These data suggest that BNP has vasopressor effects that may be independent of cGMP stimulation.1

THE NPS IN PATIENTS WITH HEART FAILURE

Pharmacological responsiveness to ANP is attenuated in patients with heart failure, whereas normal vascular and renal responses to BNP are essentially maintained in this population.67 Furthermore, the physiological effects of BNP are several times more potent than the effects of ANP, and its metabolic clearance rate is more rapid.66 Therefore, BNP would be predicted to be the more clinically useful agent, and recombinant human BNP (nesiritide) was approved recently for clinical use in decompensated heart failure.

Administration of BNP to patients with mild to severe heart failure in a number of randomized, controlled clinical trials lowered right atrial pressure, pulmonary artery pressure, pulmonary wedge pressure, mean arterial pressure, and pulmonary and systemic vascular resistance and increased cardiac index without affecting heart rate. In addition, symptomatic dyspnea and fatigue were also improved. Urine volume increased and excretion of sodium and chloride was greater than in healthy subjects.67-69 Abraham et al68 administered BNP to 16 patients with clinically decompensated left heart failure (pulmonary wedge pressure, .15 mm Hg, cardiac index, .2.5 L/min per square meter). Right- and left-sided filling pressures fell 30% and 40%, respectively. Left ventricular afterload decreased, resulting in a 28% increase in cardiac index without significantly raising heart rate. In the largest of these clinical trials (n=127), Colucci et al71 found that BNP reduced the average pulmonary wedge pressure by 10 mm Hg and increased cardiac index by 400 mL/min per square meter.

Renal function, which is often depressed in advanced heart failure, may be adversely affected by standard treatment that includes vasopressors, diuretics, and even ACE inhibitors.72 Accordingly, Jensen et al73 evaluated renal responsiveness to BNP in 19 individuals: 9 with heart failure and 10 without heart failure. Both groups showed comparable increases in GFR. Although all subjects had significant increases in urinary sodium excretion, the absolute increase was less in patients with heart failure, reflecting a blunted responsiveness of distal tubular sodium transport (Figure 2). Nevertheless, clinically significant natriuresis and diuresis persisted.

THE NPS IN PATIENTS WITH ACUTE RENAL FAILURE

The results of ANP in acute renal failure have been less clear. In a small
Figure 3. Mechanism of action of vasopeptidase inhibitors. Dual inhibition of the angiotensin-converting enzyme (ACE) and neutral endopeptidase (NEP) results in a shift in the balance resulting in inhibition of the renin-angiotensin-aldosterone system and activation of the physiologic actions of natriuretic peptides. ANP indicates atrial natriuretic peptide; AT1, antithrombin 1; BNP, brain natriuretic peptide; cGMP, cyclic guanosine monophosphate; CNP, C-type natriuretic peptide; GFR, glomerular filtration rate; NEP, neutral endopeptidase; NO, nitric oxide and PAI-1, plasminogen activator inhibitor 1.

controlled study, Rahman et al^74 administered ANP to 30 of 53 patients with acute renal failure; treated and untreated patients underwent comparable furosemide or mannitol hexanitrate therapy. Therapy with ANP was found to significantly improve creatinine clearance and reduce the need for dialysis (23% vs 52%, respectively). However in a larger, randomized clinical trial of 504 patients with acute tubular necrosis, Allgren et al^75 found no difference in the overall rate of dialysis-free survival in patients receiving ANP or placebo (43% vs 47%, respectively). In that study, a subgroup of patients with oliguric renal failure experienced significant improvements in dialysis-free survival with ANP vs placebo (8% vs 27%, respectively). This finding encouraged a larger randomized trial of ANP in oliguric acute renal failure in 222 patients. Despite the earlier findings, Lewis et al^76 showed no significant difference in dialysis-free survival at 2 or 3 weeks.

Regardless of these discouraging results, Seta et al^77 demonstrated a role for ANP in the treatment of heart failure in patients with acute renal dysfunction. In 22 patients with acute renal failure secondary to heart failure, treatment with ANP increased cardiac output and arterial oxygenation by reducing cardiac preload (right atrial and pulmonary artery diastolic pressure) and afterload (mean systolic BP), even in the absence of a diuretic response.

THE NPS IN PATIENTS WITH DIABETES

Diabetes increases the risk for development of such cardiorenal diseases as hypertension, end-stage renal disease, coronary heart disease, heart failure, stroke, and peripheral vascular disease.78-82 Patients with diabetes and hypertension are at 5 to 6 times greater risk for development of end-stage renal disease than those with hypertension alone, and lowering the BP in hypertensive patients with diabetes reduces cardiovascular and renal complications more than in nondiabetic patients.83

In patients with type 2 diabetes mellitus, ANP levels were found to be lower than in nondiabetic patients, despite the lack of difference found in extracellular fluid volume. As renal function worsens, however, plasma ANP levels rise, increasing glomerular filtration pressure by effects on arteriolar resistance. In this way, ANP might contribute to the evolution of hyperfiltration and proteinuria in diabetic nephropathy.84 Type 2 diabetes mellitus in conjunction with hypertension has been reported to be associated with elevated ANP levels in the presence of normal renal function and normal or decreased plasma renin and aldosterone levels. In this setting, ANP levels were found to rise in parallel with mean arterial BP, suggesting a counter-regulatory role.85

The widespread influence of the NPS in diverse clinical situations and the ability of this system to counterbalance the detrimental effects of chronic RAAS activation in the progression of cardiorenal disease suggests a potential role for natriuretic peptides in new therapeutic management strategies. These agents will likely to used in conjunction with ACE inhibitors/angiotensin receptor blockers^74 and/or aldosterone antagonists^81,86 in patients with diabetes, hypertension, and renal dysfunction.

EFFECTS OF NEP INHIBITION

Despite the positive results of therapeutic BNP in decompensated heart failure, its use requires intravenous administration, which limits its potential application in other chronic cardiorenal diseases. Alternatively, circulating levels of the natriuretic peptides can be effectively increased by blocking their enzymatic clearance by NEP (Figure 3). Inhibitors of NEP have been investigated for potential long-term use in such conditions as hypertension and chronic heart failure.

Candoxatril is an oral NEP inhibitor with hemodynamic effects similar, but not identical, to those of exogenously administered ANP. Although both produce venodilation, which reduces central venous pressure, and inhibit sympathetic reflex activity, ANP reduces diastolic BP, and candoxatril increases systolic BP and produces a rise in endothelin-1 levels as well.87 In healthy
subjects, 10-day administration of candoxatril raised plasma ANP levels in the short term and urinary cGMP levels in the long term, but also produced lasting cardiorenal effects.85 In patients with essential hypertension, a 28-day course of candoxatril was ineffective in lowering BP, despite a rise in circulating ANP levels.86 The failure to reduce BP in patients with essential hypertension was associated with reflex activation of the RAAS, significantly elevating plasma renin activity and aldosterone levels.87 However, blocking the RAAS with the ACE inhibitor captopril while inhibiting NEP (Figure 3) has been shown to be effective in reducing BP in rat and primate models of hypertension.88-90 Likewise, NEP inhibition alone has been ineffective in animal and human heart failure. In a rat model of heart failure produced by myocardial infarction, no differences were found in cardiac hemodynamics or cardiac hypertrophy produced by candoxatril or placebo.91 In a 10-day randomized, placebo-controlled trial of candoxatril in 24 patients with heart failure, Kentsch et al92 observed the adverse hemodynamic responses of elevated systemic vascular resistance and reduced cardiac index. Although NEP inhibition alone did not retard cardiac hypertrophy in rats with experimental heart failure, simultaneous ACE inhibition interrupted RAAS activation and blocked the adverse responses (ACE inhibition alone did not).93 Addition of ACE inhibition has also been shown to significantly potentiate renal response to NEP inhibition in dogs with pacing-induced heart failure.94

**VASOPEPTIDASE INHIBITION**

Chemical similarities are shared by ACE and NEP at their active sites, allowing development of single molecules that perform as dual enzyme inhibitors called VPIs.95 Angiotensin-converting enzyme inhibitors block production of Ang II and are recommended in the treatment of hypertension and diabetes to retard progression of renal disease. Angiotensin II promotes mesangial expansion by producing cellular hypertrophy and prolifera-

tion and induces glomerular and tubular sclerosis by increasing matrix formation. With decreasing nephron mass, Ang II causes efferent glomerular arteriolar and mesangial contraction, thus exacerbating glomerular hypertension, hyperfiltration, and proteinuria.3 Angiotensin-converting enzyme inhibitors enhance the levels of bradykinin, a potent vasodilator and natriuretic peptide, by blocking its degradation; blockade of bradykinin has led to BP elevations in a variety of experimental models.

Neutral endopeptidase inhibitors block enzymatic clearance of a number of endogenous vasoactive proteins, including the peptides of the NPs, adrenomedullin, and bradykinin, thereby elevating circulating plasma levels. These 3 substances are capable of enhancing renal function and attenuating injurious effects of Ang II on the kidney.

The complementary physiological actions of NEP and ACE inhibition (decreased Ang II levels and increased NPS peptide, adrenomedullin, and bradykinin levels) prompted development of VPIs as single agents with potential therapeutic use in cardiovascular and renal disease.95 On the basis of their dual mechanism of action, VPIs are predicted to have significantly greater cardiorenal effects than NEP or ACE inhibitors alone.96 For example, in the subtotal nephrectomy rat model of chronic renal failure, the dual NEP/ACE antagonist CGS 30440 produced greater renal protection than the ACE inhibitor benazepril hydrochloride. Blocking both NEP and ACE produced significantly greater reductions in proteinuria and fractional sodium excretion, compared with blockade of ACE alone. Although benazepril had a moderate effect on glomerular and tubular changes, CGS 30440 virtually normalized glomerular and tubular pathologic changes.97

**OMAPATRILAT**

Omapatrilat is the most clinically advanced VPI. This agent produces balanced, equipotent inhibition of NEP and ACE. Studies have produced substantial experimental and clinical evidence of the efficacy of omapatrilat in the treatment of hypertension and heart failure, with the suggestion of enhanced end-organ protection, supporting a potential role in the management of chronic cardiorenal disease for the agent.

**Renal Disease**

In a rat model of subtotal nephrectomy in chronic renal failure, Cao et al98 compared the effects of omapatrilat with those of the ACE inhibitor fosinopril sodium. Omapatrilat attenuated the rise in systolic BP in a dose-dependent manner and reduced mean BP by 25 mm Hg more than fosinopril. Proteinuria was decreased to sham-operation levels by omapatrilat, but was still above control levels with fosinopril.99 When compared with captopril in a rodent model of diabetic nephropathy, omapatrilat provided greater protection against renal end-organ damage.99 In a model of chronic renal failure, Taal et al100 administered omapatrilat or enalapril maleate to rats, beginning 4 weeks after a four-fifths nephrectomy, after the onset of hypertension and proteinuria. Although both agents normalized BP, omapatrilat produced substantially greater reductions in the long-term evolution of proteinuria and glomerulosclerosis.

In an open-label study of 89 patients with mild-to-moderate hypertension and renal insufficiency (creatinine clearance, ≤60 mL/min), treatment with omapatrilat resulted in large reductions in systolic and diastolic BP after 16 weeks, without significantly exacerbating renal dysfunction.101

**Heart Failure**

In an experimental model of heart failure produced by rapid pacing in sheep, Troughton et al102 showed that omapatrilat produces significant hemodynamic, renal, and endocrine benefits in mild and severe cardiac failure. Mean arterial and left atrial pressures fell and cardiac output increased. Urinary volume, sodium excretion, GFR, and effective renal plasma flow were all increased by omapatrilat, whereas plasma levels of Ang II and aldosterone were signifi-
cantly reduced. In chronic canine heart failure produced by rapid pacing, Chen et al found omapatrilat to produce greater natriuresis and increases in GFR than the ACE inhibitor fosinopril.

McClean and associates investigated the short- and long-term hemodynamic and neurohumoral effects of the VPI omapatrilat in human heart failure. Patients with symptomatic heart failure (n = 369) were randomized to double-blind treatment with omapatrilat for 12 weeks. Short-term 10-, 20-, and 40-mg doses of omapatrilat produced greater reductions in pulmonary capillary wedge pressure, systolic BP, and systemic vascular resistance compared with the 2.5-mg dose. After 12 weeks, higher doses of omapatrilat (20 and 40 mg) showed greater falls from baseline in PCWP and SBP than the 2.5-mg dose. The authors concluded that, in coronary heart failure, the acute hemodynamic benefit seen with higher doses of omapatrilat was associated with increases in plasma vasodilator and natriuretic peptide levels in addition to ACE inhibition. The hemodynamic benefit was maintained after 12 weeks. A large, randomized clinical trial recently compared omapatrilat and lisinopril. Results in 716 patients with New York Heart Association class II to IV heart failure and a left ventricular ejection fraction of no greater than 40% were recently reported and showed that after 24 weeks, patients randomized to receive omapatrilat experienced greater improvements in New York Heart Association functional class, especially those with class III or IV heart failure at entry. The composite end point of death, hospital admission, or discontinuation of therapy was significantly lower for omapatrilat than lisinopril. Data showed less evidence of progressive renal dysfunction in the omapatrilat group; significant elevations of serum urea nitrogen and creatinine levels occurred 2.7 and 3.4 times more often with enalapril than with omapatrilat, respectively. The Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE) study was performed to evaluate the effects of omapatrilat and the ACE inhibitor enalapril on morbidity and mortality in more than 5500 patients with New York Heart Association class II to IV heart failure. Omapatrilat was not more effective than ACE inhibition alone in reducing the risk for the combined primary end point of death or hospitalization for heart failure requiring intravenous treatment. However, the omapatrilat group had a 9% lower risk for cardiovascular death or hospitalization. Future studies are needed to evaluate the effectiveness of this drug in diabetic patients with heart failure.

Natriuretic peptides may also have effects on other components of the RAAS system not reviewed herein. Thus, future studies should address the impact of these peptides on the ACE-2 system as well as ANG I-7, to determine if natriuretic peptide mediates its beneficial effects, including reduction in oxidative stress through actions on these novel components of the renin angiotensin system.

CONCLUSIONS

Neurohormonal factors contribute to the evolution of chronic cardiorenal disease and are accountable for the progression of end-organ damage in hypertension. Diabetes is an important risk factor for development of kidney and heart disease and is responsible for the development of glomerular and tubular destruction in diabetic nephropathy and systolic and diastolic dysfunction in diabetic cardiomyopathy. The RAAS and NPS have counterbalancing effects on renal and cardiovascular function through their opposing actions on vascular tone and sodium and water balance as well as cellular hypertrophy and fibrosis.

Angiotensin-converting enzyme inhibitors block the effects of Ang II and aldosterone and are currently the first line of drug therapy in patients with hypertension, heart failure, or diabetes with microalbuminuria. A new class of drugs, VPIs, not only inhibit the RAAS but also simultaneously enhance the NPS. Experimental and clinical evidence suggests that VPIs can provide important end-organ protection in cardiorenal disease, especially in diabetic patients. Omapatrilat, which has demonstrated greater limitation of chronic renal damage than several ACE inhibitors, has performed favorably in clinical trials and may represent a potential new therapeutic strategy.

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