The Role of the Renin-Angiotensin-Aldosterone System in the Management of Heart Failure

Jo E. Rodgers, Pharm.D., and J. Herbert Patterson, Pharm.D., FCCP

Numerous clinical trials have highlighted the role of the renin-angiotensin-aldosterone (RAA) system in the development and progression of heart failure. Over 30 randomized, controlled trials have evaluated the effects of angiotensin-converting enzyme (ACE) inhibitors on morbidity and mortality in over 7000 patients with heart failure. Cumulative evidence from these trials shows that these agents significantly reduce mortality and hospitalizations, slow disease progression, and improve exercise tolerance and New York Heart Association class. The Heart Failure Society of America guidelines recommend ACE inhibitors as standard therapy for patients with left ventricular systolic dysfunction. The angiotensin receptor blockers and spironolactone offer alternative and perhaps complimentary mechanisms by which the RAA system may be therapeutically manipulated. The role of these therapies in treating heart failure is discussed.

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Numerous clinical trials highlighted the role of the renin-angiotensin-aldosterone (RAA) system in the development and progression of heart failure. Since the late 1980s knowledge regarding this pathway and the disease has grown significantly. Angiotensin-converting enzyme (ACE) inhibitors initially were recognized to have a beneficial effect by inhibiting production of angiotensin II (ATII). Soon after, angiotensin receptor blockers (ARBs) showed the ability to inhibit the effect of ATII at the receptor site. More recently, stimulation of aldosterone release by ATII was found to be manipulated by the aldosterone antagonist spironolactone. Finally, vasopeptidase inhibitors showed the ability to inhibit ACE together with neutral endopeptidase, resulting in reduced ATII and increased peptide production.

Inhibition of formation of ATII by ACE inhibitors has considerable impact on both morbidity and mortality in patients with heart failure. Alteration of aldosterone production also has a significant impact on mortality and specifically on mortality related to sudden cardiac death. Whether ARBs alone or combined with ACE inhibitors will have as significant or more
significant effect on the disease is being assessed. Also, the role of dual ACE and neutral endopeptidase (NEP) inhibitors is being studied.

**ACE Inhibitors**

**Rationale and Mechanism of Action**

The ACE inhibitors have a complex and incompletely understood mechanism of action in heart failure but appear to exert important therapeutic effects by inhibiting the RAA system. Initially, activation of the RAA system may improve cardiac output of the failing heart by increasing preload through sodium retention and volume expansion; however, prolonged activation is deleterious. Angiotensin II causes peripheral vasoconstriction, which increases afterload and diminishes cardiac output. Increases in preload from volume expansion eventually fail to augment stroke volume and produce adverse effects of volume expansion. Angiotensin II increases aldosterone release, which causes further sodium and water retention and worsens fluid overload. It also can induce hypertrophy of vascular smooth muscle and myocardium. These growth effects, which may take weeks to months to develop fully, are thought to cause long-term structural deterioration in the affected organ systems. Eccentric hypertrophy of the left ventricle promotes left ventricular failure. Therapy with ACE inhibitors prevents experimental myocyte hypertrophy that results from ATII.6

The agents have additional local actions in heart failure that are not related to hemodynamic changes and do not appear to be explained only by interference with the RAA system. Angiotensin-converting enzyme is identical to kininase II, a nonspecific enzyme responsible for degradation of bradykinin and substance P. Bradykinin has direct vasodilatory and antiproliferative effects that could benefit the failing heart. It also regulates formation of nitric oxide and two vasodilatory prostaglandins, prostaglandin E₂ and prostacyclin, which results in vasodilation and inhibition of platelet adhesion and aggregation. These effects may be of therapeutic benefit to patients with heart failure and suggest a more complicated mechanism of action of ACE inhibition in this syndrome.

**Efficacy**

**Symptomatic Heart Failure**

The ACE inhibitors prevent progression of heart failure in patients with both severe and mild to moderate symptoms. In the Cooperative North Scandinavian Enalapril Survival (CONSENSUS) study, mortality was significantly reduced with enalapril in patients with severe New York Heart Association (NYHA) class IV disease.1 Similarly, the Studies of Left Ventricular Dysfunction (SOLVD) trial reported modest, but clinically important differences in mortality and morbidity due to enalapril in patients with mild to moderate disease (NYHA classes II and III).2

**Asymptomatic Heart Failure**

The agents not only reduce mortality in patients with established heart failure, they also benefit those at risk of developing symptomatic left ventricular systolic dysfunction. In the SOLVD prevention trial, asymptomatic patients without overt heart failure but with systolic dysfunction and a left ventricular ejection fraction (LVEF) below 35% were randomized to receive enalapril or placebo.3 Whereas reductions in all-cause mortality and cardiovascular mortality were not statistically significant, the risk of the combined end point of death and development of overt heart failure was significantly reduced, as were hospitalizations for heart failure.

The ACE inhibitors are also beneficial in reducing mortality in patients with systolic dysfunction after an acute myocardial infarction. In the Survival and Ventricular Enlargement (SAVE) study, patients with left ventricular dysfunction but without overt heart failure were randomized to receive captopril or placebo.4 All patients were 3–16 days after myocardial infarction and had evidence of ventricular dysfunction (LVEF < 40%). All-cause mortality and risk of recurrent myocardial infarction were significantly reduced. In the Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardioco (GISSI-3) trial, patients treated with lisinopril within 24 hours of onset of myocardial infarction symptoms had significantly reduced mortality.5 Thus considerable evidence exists that ACE inhibitors decrease the risk of death in asymptomatic patients with systolic dysfunction after myocardial infarction.

**Development of Heart Failure in High-Risk Groups**

Clearly, the agents improve outcome among patients with left ventricular dysfunction, whether or not they have heart failure. The Heart Outcomes Prevention Evaluation (HOPE)
trial assessed the effect of ramipril in 9297 patients aged 55 years or older (mean age 66 yrs) at high risk for cardiovascular events but who did not have documented left ventricular dysfunction or heart failure. Patients had evidence of vascular disease or diabetes plus one other cardiovascular risk factor: hypertension, increased total cholesterol level, low high-density lipoprotein, cigarette smoking, or documented microalbuminuria. Patients were excluded if they were known to have heart failure or a LVEF below 40%. The trial was a placebo-controlled, two-by-two factorial design that evaluated both ramipril 10 mg/day and vitamin E 400 IU/day. The primary end point was a composite of myocardial infarction, stroke, and death from cardiovascular causes.

Compared with placebo, ramipril significantly reduced the composite outcome (p<0.001, 22% reduction). It also significantly reduced all-cause mortality (p<0.005, 16% reduction), cardiovascular mortality (p<0.001, 26% reduction), myocardial infarction (p<0.001, 20% reduction), and stroke (p<0.001, 32% reduction). Revascularization procedures, cardiac arrest, heart failure, and complications related to diabetes also were significantly reduced. Noncardiovascular mortality did not differ between groups. Subsequent review of medical records showed that the ejection fraction had been measured before randomization in 5193 patients. Of these, 8% had a reduced ejection fraction and none had heart failure. Analysis of this subgroup suggested no difference in the primary outcome in patients with and those without a history of diabetes, hypertension, microalbuminuria, coronary artery disease, or myocardial infarction. Benefits were observed whether or not patients were taking aspirin or other antiplatelet agents, β-blockers, lipid-lowering agents, or antihypertensive drugs at randomization. Despite lack of documented heart failure, many patients have cardiovascular risk factors, just as the population enrolled in this study. Thus, the results of this study are likely to apply to many patients with various degrees of the disease.

Target Dosage

In controlled clinical trials, ACE inhibitors were titrated to target dosages, typically captopril 150 mg/day, enalapril 20 mg/day, or lisinopril 20 mg/day, but they generally are prescribed at lower dosages than those shown to reduce morbidity and mortality. Target dosages achieved in individual patients in controlled trials were related to many factors and not determined in a randomized manner. This led to controversy concerning the dosage necessary for efficacy.

In the Assessment of Treatment with Lisinopril and Survival (ATLAS) study, 3164 patients hospitalized within the previous 6 months with NYHA class II–IV heart failure (LVEF ≤ 30%) were randomized to receive low-dosage (2.5–5 mg/day) or high-dosage (32.5–35 mg/day) lisinopril for at least 3 years (median 46 mo) in a double-blind, parallel study design. Previous therapy with digoxin, ACE inhibitors (89%), or vasodilators was allowed, but not mandated. The primary end point was all-cause mortality; several secondary end points included cardiovascular mortality and all-cause mortality combined with hospitalization for any reason. Compared with the low-dosage group, patients receiving the high dosage had an insignificant 8% lower risk of death (p=0.128). However, they had a significant 12% lower risk of death or hospitalization for any reason (p=0.002), 24% fewer hospitalizations for heart failure (p=0.002), and 16% fewer hospitalizations for cardiovascular reasons (p=0.05). Dizziness and renal insufficiency were more frequent in the high-dosage group, but the groups were similar in number of patients requiring discontinuation of the drug. Both dosages were tolerated.

Thus patients with heart failure should not be maintained with very low dosages of an ACE inhibitor unless these are the only dosages they can tolerate. Although the difference in efficacy of intermediate and high dosages of the agents is not likely to be large, clinical observation indicates that up titration of dosage commonly benefits patients who remain symptomatic.

Heart Failure Society of America Recommendations

Over 30 randomized, controlled trials have evaluated the effects of ACE inhibitors on morbidity and mortality in over 7000 patients with heart failure. Cumulative evidence from these trials shows that these agents significantly reduce mortality and hospitalizations, slow disease progression, and improve exercise tolerance and NYHA class. Improved clinical outcomes are evident in patients with ischemic and nonischemic etiologies of disease and for all NYHA classes including asymptomatic patients. The Heart Failure Society of America
guidelines suggest that ACE inhibitors remain the “agents of choice for blockade of the RAA system in heart failure,” and they remain the “cornerstone of standard therapy” for patients with left ventricular systolic dysfunction with or without symptomatic heart failure. Furthermore, all efforts should be made to achieve use of these agents in patients with disease caused by left ventricular dysfunction.

Angiotensin Receptor Blockers

Rationale and Mechanism of Action

Despite the efficacy of ACE inhibitors in heart failure, morbidity and mortality are common and some patients do not tolerate the drugs. Thus the need for additional well-tolerated and effective agents remains a priority. Two important class-related side effects are persistent, dry cough (fairly common) and angioedema (rare, but serious). Estimates of the frequency of cough vary greatly (0–39%), partly due to lack of standard methodology of detection in clinical trials, as well as difficulty distinguishing drug-induced cough from that due to underlying heart failure. Blockade of kininase II by ACE inhibitors results in accumulation of bradykinin in the lungs. This most likely causes cough and is thought to be responsible for the serious and potentially life-threatening angioedema. The ARBs were developed in an attempt to improve the efficacy and tolerability of agents that inhibit the RAA system. This was based on the belief that the benefits of ACE inhibitors were related to suppression of ATII formation and that side effects were related to accumulation of kinins. The ARBs do appear to be better tolerated, with reduced risk of angioedema and cough due to lack of bradykinin production. However, they seem to carry the same risk of hypotension, renal dysfunction, and hyperkalemia as ACE inhibitors.

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Originally, ACE was considered the sole enzyme associated with production of ATII. However, clinical investigation eventually established that with long-term ACE inhibition, ATII concentrations return to pretreatment levels or higher. This generated the hypothesis that ATII production may occur through several pathways other than ACE. Several non-ACE enzymes produce ATII. They generate ATII directly from angiotensin I (ATI) and are likely to be important in heart failure. By inhibiting at the receptor site, actions of ATII may be blocked regardless of pathways by which it was generated. Furthermore, the bradykinin pathway is not activated. Although bradykinin's role in cough and angioedema is understood, its role in the response to ACE inhibitors remains less clear.

Other mechanisms for reappearance of ATII during ACE inhibition are postulated. Because they are competitive inhibitors, high levels of ATI resulting from ACE inhibition may drive the continued production of ATII; or suppression of ATII may upregulate the angiotensin receptor, making it more sensitive to ATII. These effects could make traditional ACE inhibitor therapy less effective at blocking the RAA system. In contrast, ARBs would not be interfered with by these adaptations.

Theoretically, the selectivity of ARBs may be considered a benefit or a limitation. Since ARBs selectively block ATII type 1 (AT1) receptors, ATII receptors are exposed to high levels of ATII associated with their blockade. This may lead to overstimulation of unblocked, unprotected ATII receptors. Data suggest that the receptors inhibit vascular wall and myocardial cell growth, which could be beneficial. In contrast, they may promote apoptosis, which could be harmful in heart failure. Finally, ARBs may lead to increased formation of other angiotensin-derived peptides such as angiotensin (1–7) and (3–8) whose physiologic roles are under investigation.

Whether selective receptor blockade of ATII effects with ARBs will provide equal or greater improvement in heart failure symptoms and reduction in mortality and morbidity compared with ACE inhibitors is under active investigation. In placebo-controlled studies, long-term ARB therapy produced hemodynamic and neurohormonal effects similar to those of ACE inhibitors. Unlike ACE inhibitors, the agents have not shown consistent effects on symptoms or exercise tolerance. Favorable effects on myocardial remodeling in hypertrophic states were reported in some but not all animal models. In two animal studies the ARB losartan reduced left ventricular hypertrophy.

The Evaluation of Losartan in the Elderly (ELITE) substudy compared effects of an ACE inhibitor and ARB on left ventricular volumes in elderly patients with heart failure. Sixteen patients randomized to captopril and 13 to losartan underwent baseline and 48-week radionuclide ventriculograms. At 48 weeks, both drugs significantly reduced left ventricular end-diastolic volume index (losartan 135 ± 25 to 128 ± 23 ml/m², p<0.05; captopril 142 ± 25 to 131 ± 20 ml/m², p<0.01). Captopril also reduced left
ventricular end-systolic volume index (p<0.01), and there was a nonsignificant trend in losartan-treated patients. No significant difference in change in left ventricular volume was found between groups. These results do not provide a rationale for a survival benefit of losartan over captopril, but they do suggest a similar effect on myocardial remodeling.

Efficacy

Two large, placebo-controlled studies compared ARBs with ACE inhibitors. In the ELITE study, 722 patients with NYHA class II–IV heart failure (LVEF ≤ 40%) of ischemic or nonischemic origin were randomized to receive losartan up to 50 mg/day or captopril up to 150 mg/day in addition to conventional therapy for 48 weeks. Patients were required never to have received an ACE inhibitor and to have stable cardiovascular therapy. The primary end point was a safety measure of renal dysfunction, defined as an increase in serum creatinine by 0.3 mg/dl or more (≥ 26.5 mmol/L) from baseline. Composite of death and/or admission for heart failure was added as a secondary end point by protocol amendment on completion of patient participation before unblinding.

Both treatments had similar effects on the primary end point, 10.5% frequency of persisting increases in serum creatinine. Fewer patients receiving losartan discontinued therapy for adverse events (12.2% vs captopril 20.8%, p=0.002). Fourteen captopril-treated patients discontinued the drug due to cough, compared with no losartan-treated patients. Death and/or hospital admission for heart failure occurred in significantly less losartan-treated patients (p=0.075, 32% reduction). The risk reduction was primarily due to a decrease in all-cause mortality (p=0.035, 46% reduction); however, this difference no longer was present once adjustments for multiplicity of end points and interim analyses were complete. The reduction in all-cause mortality primarily was due to a reduction in sudden death. Admissions for heart failure and improvement in NYHA functional class from baseline were the same in both groups. Admission to the hospital for any reason was less frequent with losartan than with captopril (p=0.014, 26% reduction). Since mortality was not a primary end point, ACE inhibitors remained agents of first choice and ARBs were considered alternatives.

The multicenter, randomized, placebo-controlled, double-blind, parallel ELITE II study was a large-scale trial that compared the effects of ARBs and ACE inhibitors on mortality. It was designed to test the hypothesis that losartan is superior to captopril in terms of a reduction in mortality and morbidity in elderly (≥ 60 yrs) patients. Patients with NYHA class II–IV heart failure (LVEF < 40%) who had not been previously treated with an ACE inhibitor or an ARB were randomized to receive either losartan up to 50 mg/day or captopril up to 150 mg/day. The primary end point was all-cause mortality. The study was event driven (until 510 deaths active plus placebo occurred), and it was hypothesized that losartan would reduce mortality by at least 25% compared with captopril.

There were 530 deaths (250 captopril, 280 losartan). No significant differences were seen in all-cause mortality (p=0.16) and the combined end point of all-cause mortality and all-cause hospitalization (p=0.18). A slight divergence of survival curves was seen at approximately 500 days, with a slight benefit for captopril-treated patients. There was a trend toward reduction in sudden cardiac death or resuscitated cardiac arrest (p=0.08) in patients treated with captopril. Withdrawal from the study occurred in 14.7% of captopril-treated patients and 9.4% of losartan-treated patients (p<0.001).

Heart Failure Society of America Recommendations

The ARBs provide a new way to block the RAA system. They competitively inhibit ATII, binding at the site of the ATII receptor, specifically the AT1 receptor. Stimulation of this receptor results in hemodynamic effects similar to those seen with ACE inhibitors, including vasodilation, increased sodium excretion, and reduced aldosterone secretion. The ARBs are not associated with cough and angioedema apparently mediated by bradykinin and do not increase ATII levels or receptor sensitivity to ATII. Despite theoretical advantages, clinical trial data suggest that establishing the proper role of ARBs in heart failure will be a continuing and complicated process. As discussed, the Heart Failure Society of America recommends ACE inhibitors over ARBs for blockade of the RAA system, and that only patients who are “truly intolerant” to ACE inhibitors be considered for treatment with an ARB. The combination of hydralazine and isosorbide may be another alternative in ACE inhibitor-intolerant patients.
ACE Inhibitor-ARB Combination

Theoretically, combining ACE inhibitors and ARBs may offer the benefits of both classes. The combination would offer the theoretical advantage of blocking the actions of ATII while increasing bradykinin levels. It is hoped that this would result in a synergistic effect, however, less ATII and thus less ATII receptor stimulation may occur, leading to less effective therapy. Furthermore, it is unlikely that the combination would have a more tolerable side effect profile than that of ACE inhibitors alone.

Several clinical trials evaluated the combination. Initial studies were limited by short duration of follow-up, 3-6 months. During submaximum bicycle exercise, therapy resulted in a greater increase in LVEF and reduction in end-systolic volume/end-diastolic volume at peak exercise compared with placebo. The combination produced a greater increase in LVEF and treadmill exercise time than the ACE inhibitor alone. It also led to a greater reduction in blood pressure without a concomitant increase in heart rate. In patients with severe disease, the combination improved functional class and LVEF.

Combination therapy was investigated in several large clinical trials. In the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) pilot study, 768 patients with NYHA class II-IV heart failure (LVEF < 40%, 6-min walk distance < 500 meters) were randomized to one of three regimens: candesartan 4, 8, or 16 mg/day (327 patients), enalapril 20 mg/day (109), or candesartan 4 or 8 mg/day plus enalapril 20 mg (332) in addition to conventional therapy (94% ACE inhibitor, 84% diuretic, 71% digoxin, 17% b-blocker) for 43 weeks. End points in this multicenter, double-blind, placebo-controlled, parallel study were change in 6-minute walk distance, ejection fraction, ventricular volumes, neurohormone levels, quality of life (QOL), and NYHA functional class. The study was not designed or powered to assess effects on morbidity and mortality; however, it was terminated early due to an increased number of events in the treatment group. Early termination had little impact on analysis of end points as most patients had completed the study.

Overall, no difference was seen among groups with regard to NYHA class, 6-minute walk distance, or QOL. Clinical events such as death and hospitalization were not significantly different; however, death and any heart failure hospitalization was significantly lower with the combination compared with enalapril alone (p=0.037) as well as in hospitalization alone (p=0.048). There was an insignificant increase in ejection fraction and significantly lower end-diastolic and end-systolic volumes (p<0.01) and blood pressure (p<0.05) with combination therapy compared with either drug alone. The combination significantly decreased aldosterone (p<0.05) at 17 weeks as well as brain natriuretic peptide (BNP; p<0.01) at 43 weeks. Overall, candesartan was as effective, safe, and tolerable as enalapril. The combination was more beneficial for preventing left ventricular remodeling than either agent alone.

The study had several limitations. It was not a full-scale clinical trial powered to detect changes in relevant clinical parameters. At 19 weeks, patients were further randomized to metoprolol or placebo, and thus six treatment groups were evaluated. Also, several variables were analyzed. Given these limitations, it is difficult to make conclusions regarding this trial, although the trend was to favor enalapril over candesartan in head-to-head comparison.

The Study of Patients Intolerant of Converting-Enzyme Inhibitors (SPICE) was designed to assess tolerability to candesartan among 270 ACE inhibitor-intolerant patients with NYHA class II-IV disease (LVEF < 35%). Patients were randomized in a 2:1 ratio to treatment with candesartan 4 mg/day titrated to 16 mg/day if tolerated (179 patients) or placebo (91) in addition to conventional therapy (74% diuretic, 61% digoxin, 20% b-blocker) for 12 weeks. Intolerance to ACE inhibitors was due to cough (67%), hypotension (15%), or renal dysfunction (11%). The primary end point of this multicenter, double-blind, parallel study was tolerability, which was defined as the percentage of patients completing 12 weeks of treatment with the study drug. Candesartan was continued for 12 weeks in 82.7% of patients and placebo in 86.8% (NS). Titration to the target dosage was achieved in 69% and 84% of patients, respectively. Although not powered to assess these end points, there was no difference in mortality or morbidity (worsening heart failure, myocardial infarction, all-cause hospitalization, death or hospitalization for heart failure) between groups. Candesartan was well tolerated in ACE inhibitor-intolerant patients, but its effect on major clinical end points was unknown.

Several large multicenter trials are in progress.
to clarify further the role of ARBs. The Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) study will assess the drugs’ effect in ACE inhibitor-intolerant patients, its combination with an ACE inhibitor, and its impact on mortality in those with preserved systolic function.36 The Valsartan in Heart Failure Trial (ValHeFT) is assessing the agents’ effects on mortality in patients receiving an ACE inhibitor and stratified by presence or absence of β-blocker therapy.37 The Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan (OPTIMAAL) will compare the effects of losartan alone versus captopril alone.38, 39 The Valsartan in Acute Myocardial Infarction Trial (VALIANT) will compare the effects of captopril alone, valsartan alone, and valsartan combined with captopril.39 Both studies are in patients after myocardial infarction with heart failure or left ventricular dysfunction.

**Aldosterone Antagonists**

**Rationale and Mechanism of Action**

Increased renin and ATII secretions in heart failure contribute to aldosterone secretion. Elevated aldosterone levels result in sodium and fluid retention, which worsen edema. They also cause potassium and magnesium loss, which may increase the risk of arrhythmias. Finally, myocardial and vascular fibrosis increases with collagen synthesis and deposition that occur with aldosterone stimulation.40–42 Whereas ACE inhibition may transiently decrease aldosterone secretion, other means of aldosterone production exist.43 Spironolactone acts as a competitive antagonist of the aldosterone receptor, blocking its effects in myocardium, arterial walls, and kidneys.

**Efficacy**

The Randomized Evaluation Study (RALES), enrolled 1663 patients with NYHA class IV heart failure or who had experienced this degree of disease within the 6 months before randomization and had heart failure of ischemic or nonischemic etiology.44 They received spironolactone 25 mg/day or placebo in addition to conventional therapy (95% ACE inhibitor, 100% loop diuretic, 75% digoxin, 11% β-blocker) for an average of 24 months. Oral potassium supplementation was not recommended unless hypokalemia was documented, but 28% of patients were receiving supplementation at baseline. The primary end point was death from any cause. Secondary end points were death from cardiac causes, hospitalization for cardiac causes, the combined frequency of death or hospitalization for cardiac causes, and change in NYHA class. Mortality was significantly reduced in the spironolactone group (p<0.001, 30% reduction). This was attributed to a lower risk of both death from progressive heart failure and sudden death from cardiac causes. The frequency of hospitalization for worsening heart failure also was lower with spironolactone (p<0.001, 35% reduction). In addition, patients who received spironolactone had significant improvement in symptoms of heart failure, as assessed on the basis of NYHA functional class (p<0.001). However the effect on clinical symptoms must be defined more clearly, as patients who died during follow-up were assigned a NYHA IV classification in the analysis.

Gynecomastia was a common side effect, reported in 10% of men who were treated with spironolactone, compared with 1% of men in the placebo group (p<0.001). The frequency of serious hyperkalemia was minimal in both groups, but data on baseline potassium level and renal function await publication. Of importance, this population may not be representative of all patients with advanced heart failure given a baseline systolic blood pressure of 123 mm Hg and LVEF of 26%. Data on baseline renal function and serum potassium concentration have not been reported but are important in assessing which patients are likely to avoid excessive hyperkalemia with this agent. The potential for excessive diuresis when spironolactone is combined with intense use of loop diuretics in patients with advanced heart failure remains to be defined. Despite the relatively large scale of RALES, some caution concerning widespread application of spironolactone therapy seems appropriate.

Heart Failure Society of America Recommendations

By blocking directly at the receptor site, spironolactone may prevent detrimental effects of aldosterone production from angiotensin stimulation or other sources. Given compelling study results, the Heart Failure Society of America recommends considering low dosage of 12.5–25 mg once/day for patients with severe, systolic heart failure (recent or current NYHA
class IV) despite standard therapy. Given the unusual RALES population, the society recommends that patients considered for therapy with spironolactone should have a normal serum potassium level (< 5.0 mEq/L) and adequate renal function (creatinine < 2.5 mg/dl). Serum potassium concentration should be monitored at regular intervals and specifically within the first week of therapy. It also should be measured in any situation that may alter the value, including a change in spironolactone dosage, change in renal function, or addition of a concomitant drug that may affect potassium balance (ACE inhibitor). If possible, supplemental potassium should be lowered or eliminated altogether.

Table 1 summarizes clinical trials of ACE inhibitors, ATII receptor blockers, and aldosterone antagonists.

### Rationale and Mechanism of Action

Many recent advances in heart failure focused on decreasing the activation of endogenous
vasoconstrictor systems (RAA system) rather than enhancing the response to endogenous vasodilator mechanisms. By inhibiting the breakdown of vasodilatory substances, specifically natriuretic peptides, favorable hemodynamic and neurohormonal effects may be achieved, accompanied by attenuation of ventricular remodeling and prolonged survival. Evidence to support this emerged from clinical trials with the vasopeptidase inhibitor omapatrilat, which simultaneously blocks the activity of both ACE and NEP enzymes.

Angiotensin-converting enzyme inhibition provides clinical benefits but also prevents counterregulatory effects by the RAA system, which could limit the benefit of NEP inhibition alone. Inhibition of NEP results in accumulation of several peptides, including atrial natriuretic peptide (ANP) and BNP. Activation of the RAA system results in vasoconstriction, sodium retention, and increases in aldosterone release, cellular growth, and sympathetic nervous system activity; activation of the natriuretic peptide system results in the opposite physiologic effects. Specifically, release of ANP and related peptides causes vasodilation, sodium excretion, decreased aldosterone release, decreased cellular growth, and inhibition of sympathetic nervous system activation. In a preliminary study in patients with heart failure due to systolic dysfunction, selective inhibition of NEP was not successful.45 One explanation for the failure could be that the therapy activates the RAA system, which counteracts any potential antihypertensive effect.

Vasopeptidase inhibitors were developed in an attempt to overcome this limitation of selective NEP inhibition by providing dual enzyme inactivation of ACE and NEP. Omapatrilat combines equal ACE and NEP inhibition. Studies in normotensive humans treated with omapatrilat reported both a decline in serum ACE activity and an increase in urinary ANP levels.46

Animal models of hypertension show the antihypertensive effects of omapatrilat in a wide variety of conditions.47 Data from an animal model of postmyocardial remodeling suggest that the drug maintains bradykinin activity in incubated tissue to a higher degree than ACE inhibition, consistent with findings that NEP plays an important role in bradykinin degradation.48

Human data established that omapatrilat is an effective antihypertensive in a wide variety of clinical settings.49-50 The drug significantly reduces blood pressure across the wide spectrum of hypertensive patients including African-Americans, the elderly, and salt-sensitive individuals. It exerts favorable effects in animal models of heart failure, and preliminary evidence suggests beneficial effects in patients with heart failure due to systolic dysfunction.51, 52 Omapatrilat appears to improve clinical status and cardiac function by improving neuroendocrine status, natriuresis, diuresis, and afterload reduction.53

**Efficacy**

The IMPRESS trial was a randomized, double-blind, parallel trial of 573 patients with NYHA class II-IV heart failure (LVEF ≤40%) comparing the impact of omapatrilat and an ACE inhibitor on functional capacity (exercise tolerance and functional class) and comorbidity (risk of death and hospitalization).54 Patients received omapatrilat 40 mg/day (289 patients) or lisinopril 20 mg/day (284 patients) over 24 weeks. All patients were taking an ACE inhibitor before randomization, and 30% were taking a β-blocker. The primary end point was improvement in maximum exercise treadmill test at week 12. Secondary end points included death and comorbid events indicative of worsening heart failure. There was no significant difference in exercise tolerance between omapatrilat and lisinopril (+24 sec and +31 sec, respectively). Among patients with NYHA class III-IV heart failure, the class improved significantly (p<0.035). However, when patients with NYHA class II were included, the difference was not significant. The combined end point of mortality and hospitalization for worsening heart failure was insignificant; however, there was a trend favoring omapatrilat (p=0.052). The composite end point of death, admission, or discontinuation of study drug for worsening heart failure was significantly reduced with omapatrilat (p=0.035). Although both therapies were fairly well tolerated, there were fewer cardiovascular side effects in the omapatrilat group (p=0.04).

Assessment of the 24-week IMPRESS study and a 52-week safety study (CV13-018) combined the results of both trials (1242 patients) to compare the effects of the two agents.55 A significant reduction in the combined end point of death and hospitalization for heart failure was seen (p=0.03, 28%) and an insignificant reduction in death alone. The frequency of adverse effects was similar; however, fewer cardiovascular events, incidents of renal dysfunction, and
marked elevations in creatinine occurred with omapatrilat. Hypotension was greater in omapatrilat-treated patients (11% vs 6.5%) and syncope was more frequent in lisinopril-treated patients (5.1% vs 1.4%). Angioedema occurred in one patient receiving lisinopril and no patients receiving omapatrilat.

The Omapatrilat versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE) trial is comparing the effects of omapatrilat 40 mg/day and enalapril 20 mg/day in 4420 patients receiving omapatrilat.

In one patient receiving lisinopril and no patients (5.1% vs 1.4%). Angioedema occurred in omapatrilat-treated patients (11% vs 6.5%) and hypotension was greater in omapatrilat. Marked elevations in creatinine occurred with omapatrilat. The HOPE Study Investigators. Update on RAA SYSTEM AND HEART FAILURE. Rodgers and Patterson 3775

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