

## Neurohormonal Antagonism in Heart Failure:

### What Is the Optimal Strategy?

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#### Abstract

Pharmacologic management of chronic heart failure rests on appropriate volume management followed by neurohormonal antagonism. Despite the rationale for neurohormonal antagonists, their use remains low.

Definitive studies establish that neurohormonal antagonists are effective across the spectrum of disease, from the early Stage A patient at risk of developing structural heart disease and symptomatic heart failure to the Stage D patient with symptoms at rest.

Although many investigators and clinicians seem focused on the next new scientific breakthrough, published studies delineate strategies that will reduce death and disability for those at risk and those with symptomatic chronic heart failure. In essence, the broad use of neurohormonal antagonists, consistent with the reports of large-scale trials that have been reported, will markedly reduce the risk of disease progression and death. Overall prognosis however remains poor.

We review the data from these trials to encourage clinicians to use these proven neurohormonal antagonists in optimizing therapeutic strategy.

**Key Words:** Chronic heart failure, neurohormonal antagonism, treatment.

#### Introduction

CHRONIC HEART FAILURE is classically described as a clinical syndrome in which abnormalities of left ventricular (LV) function and neurohormonal regulation lead to progressive functional limitation, fluid retention, and increased risk of death. Coronary artery disease and hypertension are the two most common triggers leading to the development of heart failure, with subsequent activation of neurohormonal systems leading to progression to the symptomatic stage of heart failure (1). The role of these neurohormonal systems is well described; although serving an important role in maintaining circulatory homeostasis in the short term, chronic activa-

tion is toxic to the myocardium — worsening hemodynamic and clinical status (2).

Over the past two decades, numerous studies have demonstrated that neurohormonal antagonists slow the progression of heart failure, improving symptoms and reducing the risk of death (3–14). Therefore, patients with heart failure should receive at least two neurohormonal antagonists, angiotensin-converting enzyme (ACE) inhibitors and  $\beta$ -blockers. Recent data suggests potential utility for an additional class of neurohormonal antagonist, the angiotensin receptor blockers (ARB) (15, 16). However, recent studies suggest a potentially adverse interaction when additional neurohormonal antagonists are used in conjunction with ACE inhibitors and  $\beta$ -blockers (16, 17). This observation is not unique to this angiotensin receptor blocker, as centrally acting sympatholytic moxonidine was associated with increased risk of death and the  $\beta$ -blocker bucindolol could not better placebo in a large-term, adequately powered clinical trial (13, 18, 19). In general, drug development programs have focused on antagonizing deleterious neurohormones (and cytokines). Yet such agents directed against endothelin proved risky (20), and cy-

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Adapted from a Grand Rounds presentation to the Department of Medicine, Mount Sinai School of Medicine, New York, NY, on January 24, 2000, and updated as of September 22, 2003.

tokine antagonists offer no benefit (21). In contrast, aldosterone inhibitors appear promising (22, 23). In patients with left ventricular dysfunction and heart failure after a myocardial infarction, eplerenone, an aldosterone inhibitor, reduces the risk of death and major morbidity (23).

A major problem is that the standard definition of heart failure focuses on patients whose disease has advanced to the symptomatic phase, while the disease process leading up to this point includes far greater numbers of patients; those who are at risk of developing overt heart failure and are at risk of sudden death. Accordingly, the recent AHA/ACC guidelines focus attention on this larger population of patients at risk, specifically those with coronary disease, hypertension, dyslipidemia and diabetes by introducing a new classification system for heart failure (24). These four stages of heart failure, and the recognized progressive course for those who are at risk reinforce the importance of determining the optimal strategy for neurohormonal antagonism as we attempt to improve the natural history of the syndrome (Table 1). Our purpose is to review the effects of the available neurohormonal antagonists in order to propose a strategy for optimal neurohormonal antagonism.

### Adrenergic Antagonists

#### Clinical Trials

There is no longer doubt that adrenergic antagonism is standard care for patients with heart failure.  $\beta$ -blockers reduce symptoms, slow disease progression and decrease the risk of death (8, 9, 13, 25, 26).  $\beta$ -blockers are effective for patients with heart failure due to ischemic or non-ischemic etiologies (8, 9, 26), and improve outcomes whether patients are minimally symptomatic or suffer from advanced disease (8, 9, 13, 14, 25, 26). However, not all agents that antagonize the sympathetic nervous system (SNS) have the same effects (13, 18, 19). Therefore, one cannot assume that all adrenergic antagonists are interchangeable for the treatment of heart failure, and in our climate of evidence based medicine, we should select the agents proven to be effective in randomized controlled clinical trials. The  $\beta$ -blockers that are currently available differ in their specificity for  $\beta$ -1 and  $\beta$ -2 receptors, with some (e.g., metoprolol and bisoprolol) considered relatively  $\beta$ -1 receptor selective while others (e.g., carvedilol) are relatively non-selective. Recent data suggests that metoprolol may be less  $\beta$ -1 selective than pre-

**TABLE 1**  
*Stages of Heart Failure, Adapted from AHA/ACC Guidelines (24)*

Stage	Description	NYHA	Clinical Clues
A	Patients at high risk of developing HF.	Not applicable	Coronary artery disease, hypertension, diabetes, dyslipidemia, family history of cardiomyopathy.
B	Patients who have structural heart disease but have never manifested signs or symptoms of HF.	I	Left ventricular hypertrophy (by ECG or echo), valvular disease, past myocardial infarction.
C	Patients who have current or prior symptoms of HF.	II–III	Dyspnea, fatigue, exercise intolerance, prior HF hospitalization.
D	Patients with advanced structural heart disease and marked symptoms of HF at rest.	IV	End-stage, awaiting transplant, receiving palliative care.

viously considered. In a controlled trial comparing carvedilol to metoprolol succinate, patients had doses titrated toward target, and at each visit, had an assessment of  $\beta$ -2 antagonism via measurement of glucose and potassium during terbutaline infusion. This study demonstrated that 100 mg of metoprolol succinate is mildly selective and 200 mg not selective at all relative to carvedilol 12.5 and 25 mg bid, respectively (27). Several  $\beta$ -blockers also have properties in addition to  $\beta$ -blockade; for example, carvedilol has  $\alpha$ -1-blocking (vasodilator) and antioxidant properties and bucindolol also causes vasodilation, although the mechanism of this is as yet unclear. Although it is not known whether these pharmacological differences result in clinically meaningful differences between the three  $\beta$ -blockers proven to improve clinical outcomes in heart failure — carvedilol, metoprolol succinate and bisoprolol (Table 2) — the COMET study demonstrated significant clinical benefits from carvedilol compared with metoprolol tartrate (33).

**TABLE 2**  
*Beta-Blockers for Heart Failure*

**A. Beta-Blockers Proven Effective in Heart Failure**

Drug	Start Dose	Target Dose	Other Indications
Carvedilol	3.125 mg BID	25–50 mg BID	HTN, post-MI LV dysfunction
Metoprolol succinate*	12.5 mg QD	200 mg QD	HTN, angina
Bisoprolol	1.25 mg QD	10 mg QD	HTN, angina

**B. Beta-Blockers Used in Heart Failure Trials**

Drug	Start Dose	Studied Dose	Other Indications
Metoprolol tartrate	6.25 mg BID	50 mg BID-TID	HTN, angina, acute MI

**C. Beta-Blockers Not Evaluated in Large-Scale Heart Failure Trials**

Drug	Indications
Atenolol	HTN, angina, acute MI
Propranolol	HTN, angina, migraine, atrial arrhythmias

HTN = hypertension, CAD = treatment of acute and/or chronic coronary disease, LVD = left ventricular dysfunction, CHF = chronic heart failure, MI = myocardial infarction. \* = under FDA review for heart failure indication.

**Drug Selection**

Although the initial randomized studies comparing carvedilol and metoprolol were not sufficiently powered to show a clinical difference in outcome, the surrogate endpoints evaluated were intriguing (28–31). Metra and colleagues evaluated the effects on ventricular performance and exercise hemodynamics in 150 patients randomized to receive carvedilol or metoprolol for up to 44 months. When reassessed after 13–15 months of treatment, although both groups improved, the carvedilol-treated patients had significantly greater increases in LV ejection fraction at rest, and in LV stroke volume and stroke work during exercise, and also had greater decreases in mean pulmonary wedge pressure, both at rest and during exercise compared with metoprolol. In contrast, the metoprolol group showed greater increases in maximal exercise capacity than the carvedilol group (31). Di Lenarda evaluated the effects of carvedilol in 30 patients who remained limited by symptoms of heart failure and ventricular dysfunction after at least 1 year of treatment with metoprolol. In this open-label study, ejection fraction improved significantly by 1 year after changing from metoprolol to carvedilol (30). In contrast, two studies that randomized patients to carvedilol or metoprolol found no differences in hemodynamics (28, 29) or measures of oxidative stress (28), although carvedilol significantly reduced left ventricular end-diastolic dimension to a greater extent (29). It should be noted that the surrogates used in

these studies, however, are not necessarily predictive of clinical effects. This is even more apparent when one realizes that the adrenergic antagonist moxonidine reduces sympathetic activation (32) yet increases the risk of death (19).

Carvedilol, metoprolol and bisoprolol all improve well-being and reduce the risk of death. However, the Carvedilol or Metoprolol European Trial (COMET) allows us to be more definitive in prioritizing the utility of particular  $\beta$ -blockers for the treatment of heart failure. This study compared carvedilol (25 mg BID) to metoprolol tartrate (50 mg BID) and demonstrated that carvedilol reduced the risk of death significantly better than metoprolol tartrate (33). Some may find it difficult to apply these data to clinical practice, since metoprolol tartrate was studied but metoprolol succinate is the formulation proven to be effective in heart failure.

Despite the multitude of ways the data can be interpreted, a simple view may be most useful for clinical practice. Since carvedilol has proven to be better than other  $\beta$ -blockers, carvedilol must be viewed to be superior within its class. Perhaps another  $\beta$ -blocker might yet be proven to be as good or better. Therefore, based on the available data (33), all heart failure patients should be treated with carvedilol. Alternatively, since the heart rate reduction with carvedilol and metoprolol tartrate were similar over the course of the study, and therefore the drugs were dosed for comparable  $\beta$ 1 blockade, the superiority of carvedilol may reflect the importance of  $\beta$ 2 and  $\alpha$ 1 blockade.

## Metabolic Effects

Carvedilol produces different metabolic effects than metoprolol (34) and atenolol (35), which may be of clinical relevance considering the link between insulin resistance and clinical outcomes (36–38). The mechanism of this difference appears to relate to the  $\alpha$ -1 antagonism of carvedilol (39). If this effect were independent of the anti-hypertensive effects of these agents, then it could prove quite important, as non-diabetic patients with mild-to-moderate heart failure can be insulin resistant (40–43). The COMET trial reported a 22% reduction in the development of diabetes in patients with heart failure treated with carvedilol compared to metoprolol ( $p=0.04$ ) (44), supporting the findings of these smaller mechanistic studies (34, 35).

## Strategies for Clinical Practice

$\beta$ -blockers should be administered to all patients with symptomatic heart failure when they are stabilized on oral medications (13, 45, 46) as well as those with left ventricular dysfunction after a myocardial infarction (14). Background therapy should include diuretics as required, digoxin and ACE inhibitors. This strategy could extend to asymptomatic patients with only mild LV dysfunction, based on the data in patients treated after a myocardial infarction (14) (stage B heart failure), the known pathophysiology of the disease (1), and the risk that the first manifestation of disease progression can be sudden death.

Patients with severe heart failure who require inotropic agents intravenously or other assist devices should be started on  $\beta$ -blocker therapy when weaned from intravenous medications and stabilized on oral agents (13). Starting doses of  $\beta$ -blockers should be as low as possible, with gradual increases over several weeks or months towards the target doses used in the large-scale trials (47). In contrast to ACE inhibitors, for which it took over 15 years of use before dose ranging trials were completed (48), we know the minimally effective dose for at least one  $\beta$ -blocker, carvedilol. Although this dose-ranging study with carvedilol is supportive of increasing the dose to 25 mg BID, most of the relevant endpoints were significantly improved even at the lowest dose studied, 6.25 mg BID (49). While it is tempting to conclude that any dose of any  $\beta$ -blocker that is hemodynamically active would

be acceptable, this may not be a safe conclusion to apply to those  $\beta$ -blockers where dose-ranging data are not available, and therefore the lack of such data with metoprolol and bisoprolol could seem to be a problem. However, each of the drugs has been shown to be effective in clinical trials with a strategy of increasing the dose to that which is maximally tolerated, and this should be the plan in clinical practice. On average, patients tolerate the up-titration to target doses well. During this initiation phase, sicker patients are at higher risk of developing fluid retention and symptomatic hypotension if the dose is escalated rapidly, at weekly intervals (50), but the risk of these side effects is not increased when the dose is increased more gradually and in fact, risk of worsening heart failure is reduced within the first weeks of administration (51). In most patients, this is not a major problem and management of these side effects is generally successful when the rate of dose escalation is slowed and background therapies are adjusted (47). In fact,  $\beta$ -blockers can be safely administered to patients with symptoms at rest or with minimal exertion, as demonstrated in the Copernicus trial (13).

## ACE Inhibitors

### Clinical Trials

ACE inhibitors are a proven therapy for patients with ventricular dysfunction, whether symptomatic or not (3, 5–7, 52). Recent studies have supported the utility of ACE inhibitors in limiting the initial myocardial injury that leads to heart failure, both in the setting of acute myocardial infarction (53–56) and in those at risk of developing heart failure (52). The Heart Outcomes Prevention Evaluation (HOPE) study provided compelling data to use ACE inhibitors more widely. The trial assessed the role of the ACE inhibitor ramipril on cardiovascular events, survival and the development of heart failure in 9,533 patients. The population studied did not meet the “standard” criteria for ACE inhibitor therapy: their blood pressure was controlled and ventricular function was normal, yet they were at a high risk for cardiac events (being either patients with vascular disease or diabetics with at least one additional coronary risk factor). The primary endpoint of cardiovascular death and major morbidity was reduced by 22% and the risk of heart failure by 23% (52). These data mandate that

ACE inhibitors become first-line therapy for patients with vascular disease, including patients with cerebrovascular or coronary artery disease, in addition to those with the traditional coronary risk factors.

### Drug Selection

The debate over potential superiority of some agents over others focuses on pharmacokinetic and pharmacodynamic differences because there are no comparative studies with outcomes data. Those agents with longer half-lives would appear to afford a dosing advantage, resulting in better patient compliance. Other agents have greater distribution into tissues, potentially affecting the local renin-angiotensin-aldosterone system (RAAS) in the vascular endothelium and myocardium. In a comparative study, a tissue binding ACE inhibitor had a significantly greater effect on peripheral arterial vasodilation compared with a non-binding agent (57). Unfortunately, there are no studies that address the clinical impact of this pharmacologic property, although the tissue binding properties of an ACE inhibitor can be quite important.

Two lines of evidence suggest advantages of tissue avidity. In sudden death and acute myocardial infarction, angiotensin II and activated immune cells co-localize to the site of plaque rupture (58). This phenomenon increases the activation of the metalloproteinases that promote plaque rupture (59). Therefore, if an ACE inhibitor could penetrate into the tissue and interrupt the production of angiotensin II, it could yield a clinical benefit. Such a benefit has not been demonstrated and is not being addressed by any ongoing trial. However, the possibility of benefit cannot be ignored. An additional advantage for a tissue avid ACE inhibitor relates to the frequency of administration. For example, ramiprilat, the active form of ramipril, has only a 2–4 hour half-life. This would suggest the need for TID dosing, except that ramiprilat has triphasic elimination kinetics, meaning that following absorption into the plasma and rapid distribution into tissues, drug clearance from the plasma is followed by release of ramiprilat from the tissues back into the circulation. This results in an effective half-life of over 50 hours (60). Therefore, even without clinical outcomes data, tissue avidity of an ACE inhibitor can be an important factor in drug selection. Agents that bind to the tissues in this fashion can realize an effective half-life long enough to be ad-

ministered once daily, as would be the case with a non-tissue avid agent with a much longer half-life, such as lisinopril. It should be noted, however, that those with a longer half-life may be less likely to cause dizziness and hypotension due to their gradual onset and more constant hemodynamic effects over the course of the day. Either strategy permits once-daily dosing, which would improve patient compliance. Once an agent is chosen, the target dose is generally the maximum tolerated. However, there are no general rules that can be applied to all patients to determine when the maximum tolerated dose has been achieved, especially when blood pressure starts to drop or functional azotemia develops. The standard recommendation has been to use the doses shown to be effective in randomized clinical trials (45) (Table 3).

Recently, two large studies evaluated the clinical effects of low- compared with high-dose ACE inhibitor therapy. The NETWORK study evaluated the effects of 2.5, 5 and 10 mg BID of enalapril in 1,500 patients with chronic heart failure over 6 months. The study demonstrated no difference between the doses used in terms of all-cause mortality (61). The Assessment of Treatment with Lisinopril and Survival (ATLAS) (48) study enrolled 3,164 patients, followed for a mean of 3.5 years, comparing 2.5–5 mg daily of lisinopril with 32.5–35 mg daily. Although Atlas failed to demonstrate a difference in its primary endpoint, all-cause mortality, the 12% reduction in the combined endpoint of death and hospitalization supports the use of higher doses when tolerated. Perhaps most interestingly, patients on high-dose lisinopril tolerated the drug well and had a lower incidence of cough (48). This is likely due to improvement in cardiac filling pressures at higher doses reducing the frequency of cough caused by pulmonary hypertension and congestion. This would indicate that any patient experiencing cough with an ACE inhibitor should have the dose increased as aggressively as possible to determine whether they are able to tolerate ACE inhibition and realize its clinical benefits. If this strategy is not effective, the dose of diuretics can be increased. Doubling the dose once or even for several days can be sufficient to reduce subclinical congestion, and if weight drops and the cough still does not improve, then it becomes more likely that this is an ACE inhibitor-induced cough. Importantly, cough is common in heart failure patients, but review of clinical trials of ACE inhibitors reveals that the placebo-treated patients experience cough al-

**TABLE 3**  
*Antagonists of the Renin-Angiotensin-Aldosterone System for Heart Failure*

**A. Agents Proven Effective in Heart Failure and/or Left Ventricular Dysfunction**

Drug	Start Dose	Target Dose	Other Indications
Captopril	6.25 mg TID	50 mg TID	HTN
Enalapril	2.5 mg BID	20 mg BID	HTN
Lisinopril	2.5 mg QD	40 mg QD	HTN
Quinapril	5 mg BID	20 mg BID	HTN
Ramipril	1.25 mg QD	10 mg QD	HTN, post-MI
Trandolapril	1 mg QD	4 mg QD	HTN, LVD post-MI
Zofenopril	7.5 mg QD	30 mg QD	HTN
Spirololactone	12.5 mg QD	25–50 mg QD	Ascites
Valsartan	80 mg BID	160 mg BID	HTN, HF if ACE inhibitor intolerant
Eplerenone	25 mg QD	50 mg QD	HTN, LVD post-MI

**B. Agents Studied in Heart Failure But Not Proven Effective in Large-Scale Trials**

Drug	Start Dose	Maximum Dose	Other Indications
Fosinopril	5 mg QD	40 mg QD	HTN
Benazepril	5 mg QD	20 mg QD	HTN
Perindopril	2 mg QD	16 mg QD	HTN
Losartan	25 mg QD	50 mg QD	HTN
Irbesartan	75 mg QD	300 mg QD	HTN
Candesartan	4 mg QD	16 mg QD	HTN

**C. Agents Used Clinically But Not Evaluated in Large Scale Heart Failure Trials**

Drug	Indications
Moexipril	HTN
Tasosartan	HTN
Eprosartan	HTN
Telmisartan	HTN

HTN = hypertension, CAD = treatment of acute and/or chronic coronary disease, LVD = left ventricular dysfunction, CHF = chronic heart failure, MI = myocardial infarction.

most as frequently (3, 6). Although ATLAS can be interpreted as evidence to treat patients with low doses of ACE inhibitors, many patients do feel better at higher doses. In clinical practice, we should follow the strategy from the large-scale, randomized, placebo-controlled trials that proved the effectiveness of ACE inhibitors, i.e., to titrate the dose to the maximum tolerated over several weeks. In so doing, we will be providing the maximum benefit of neurohormonal blockade.

**Metabolic Effects**

ACE inhibitors are also useful for correcting metabolic abnormalities in heart failure patients. Insulin resistance diminishes following the administration of ACE inhibitors (62–64), this is important in heart failure patients because of the tendency for diuretics to worsen insulin resistance (63–65). This corrective effect occurs independently of angiotensin II activity,

and may represent an advantage of ACE inhibitors over angiotensin receptor blockers (62, 66). Additionally, ACE inhibitors reduce proteinuria (67), and slow the progression to renal failure for hypertensives — a common comorbidity in heart failure patients. Recent trials with the angiotensin receptor blockers losartan (68) and irbesartan (69) demonstrate similar effects in type 2 diabetics, indicating that the mechanism relates in large part to antagonism of angiotensin II.

**Strategies for Clinical Practice**

Treatment guidelines for the use of ACE inhibitors in clinical practice describe starting doses, target doses, and the side effects (45, 46). Two factors that often lead to inappropriate drug withdrawal deserve particular attention. First, modest azotemia should not necessarily indicate impending renal failure or the presence of significant renal artery stenosis. As an-

giotensin II vasoconstricts the efferent arteriole in the glomerulus, a reduction in the amount of angiotensin II produced through ACE inhibition or angiotensin receptor blockade should decrease glomerular filtration, leading to “functional” azotemia (70). In this case, a slight rise in creatinine of 0.2–0.5 mg/dL should be accepted if it remains stable thereafter. The level of tolerance becomes less in patients with a baseline creatinine above 2.0 and even less above 2.5 mg/dL. If creatinine level becomes markedly elevated, the diagnosis of renal artery stenosis should be pursued. Second, lack of a therapeutic benefit after only a few days or weeks should not lead to drug withdrawal, as these agents produce short-term effects that may vary greatly from their long-term effects (71), and they may not produce clinically measurable effects for up to 3 months (72). Additionally, these agents can prevent progression of disease and reduce the risk of death, even in the absence of improved quality of life (3). Patients more likely to experience side effects early in treatment can be identified; e.g., sicker patients with hyponatremia (73), diabetics (74), those with marked renal dysfunction (75), or those with marked activation of the RAAS, including patients who have recently undergone a large volume diuresis. Those patients with low right atrial pressures ( $\leq 12$  mm Hg) and preserved renal function ( $<1.5$  mg/dL) appear twice as likely to improve clinically than those with high right atrial pressure and abnormal serum creatinine levels (76).

### Angiotensin Receptor Antagonists

#### Rationale

In contrast to ACE inhibitor therapy, which prevents the adverse effects of angiotensin II by blocking its synthesis via ACE, angiotensin receptor blockers prevent angiotensin II from acting on the cell by selectively blocking AT<sub>1</sub> receptors. This prevents vasoconstriction, sodium retention, hypertrophy, and fibrosis. Additionally, the effects of angiotensin II as a positive inotrope and a stimulus for the secretion of endothelin and the release of norepinephrine would be blocked (77). Angiotensin receptor blockade effectively treats hypertension and improves cardiac filling pressures in patients with heart failure (78, 79). Since angiotensin II can be produced by enzymatic pathways in addition to the ACE pathway (77), levels of angiotensin II begin to rise months or years after

starting therapy with an ACE inhibitor (80, 81). Therefore, angiotensin receptor blockers may be a more direct approach to blocking the effects of RAAS system activation in patients with heart failure.

#### Clinical Trials

Angiotensin receptor blockers initially were evaluated as an alternative to ACE inhibitors for patients with heart failure, based upon the expectation that they would prove as effective with less azotemia and a lower incidence of cough. While the hemodynamic effects were similar to that seen with ACE inhibitors, the Evaluation of Losartan in the Elderly (ELITE I) trial was the first study to address the clinical impact of these agents. This study appeared to show a reduction in the risk of sudden death with losartan compared with captopril, but the study was not definitive, as this analysis was a secondary endpoint for which the statistical power was not very robust (82). A second trial, ELITE II, attempted to confirm the observation, but the results appeared to favor the ACE inhibitor, although the differences did not reach statistical significance (83). The investigators concluded that, of the two classes, ACE inhibitors remain the therapy of choice. In the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) study, candesartan was evaluated relative to enalapril and the combination. This study was not designed to assess the effect on clinical endpoints, but rather on neurohormonal activation and LV remodeling. However, patients who received angiotensin receptor blockers did not appear to respond as well as those on enalapril alone, although there were no significant differences (17). These trials did not address an equally important issue, that of whether angiotensin receptor blockers are useful when added to ACE inhibitor therapy.

Two trials were designed to assess the safety and efficacy of combined ACE inhibitor and angiotensin receptor blocker therapy in chronic heart failure, Val-HeFT, the recently completed study using valsartan (16) and Charm, which recently reported its results (84). The results of Val-HeFT support the use of this angiotensin receptor blocker in patients with chronic heart failure who are intolerant of ACE inhibitors (44% reduction in the combined risk of death or hospitalization), but raise questions about the addition of this therapy in patients already receiving ACE inhibitors and  $\beta$ -blockers.

For these patients, the addition of valsartan was associated with a trend toward increased risk of death or hospitalization (RR = 1.18,  $p = \text{ns}$ ) and a trend towards higher risk of death (RR = 1.41,  $p = \text{ns}$ ) (16). Although these estimates cannot be considered definitive, due to the nature of subgroup analyses and the level of statistical significance, the trends are strong enough to warrant restraint when considering combination therapy with  $\beta$ -blockers, ACE inhibitors and ARBs, in particular when the ARB is valsartan. Such perspective may be judicious based on the contrasting finding of safety using candesartan in combination with  $\beta$ -blockers and ACE inhibitors, as reported in the CHARM study (84). Candesartan was associated with a strong trend toward reduction in the risk of death (0.91, 95% confidence intervals 0.83–1.00,  $p=0.55$ ) along with significant decrease in the risk of cardiovascular death (0.88, 95% CI 0.79–0.97,  $p=0.012$ ) and fewer heart failure hospitalizations (0.77, 95% CI 0.70–0.84,  $p<0.0001$ ) (84).

### Strategies for Clinical Practice

Currently angiotensin receptor blockers are used in heart failure patients intolerant to ACE inhibitors or those with side effects deemed untenable. As none of these agents has been shown to improve clinical outcomes in addition to ACE inhibition and  $\beta$ -blockade, no angiotensin receptor blocker should be considered standard therapy in the treatment of heart failure except in the case of ACE inhibitor intolerance.

#### Aldosterone Antagonists

Activation of the RAAS leads to progression of heart failure through the effects of angiotensin II as well as via aldosterone. The effects of aldosterone are similar to angiotensin II, especially in terms of volume expansion and myocardial fibrosis (85). Its contribution to disease progression was confirmed by the beneficial effects of anti-aldosterone therapy with spironolactone in patients with advanced heart failure (22). In this study, patients with recent class IV symptoms who were still affected by NYHA class III–IV symptoms after optimal therapy were treated with spironolactone or placebo. Spironolactone significantly reduced the risk of death in this population. Eplerenone was recently approved by the FDA for the treatment of hypertension and was proven to reduce the risk of death and major morbidity in pa-

tients with left ventricular dysfunction after a myocardial infarction (23).

There are concerns about the use of spironolactone. First, there are no data demonstrating the safety or effectiveness in patients with mild heart failure or in those with ventricular dysfunction after a myocardial infarction. Second, we do not know that this agent is safe when added as a third neurohormonal antagonist to the regimen now considered standard (i.e., an ACE inhibitor and a  $\beta$ -blocker). Although relatively few patients in the Randomized Aldactone Evaluation Study (RALES) were receiving  $\beta$ -blockers, it appears from this post-hoc subgroup analysis that the addition of spironolactone to ACE inhibitor and  $\beta$ -blocker therapy would be a beneficial strategy. Nonetheless, this should not be considered proven. Additionally, patients treated with a  $\beta$ -blocker and an ACE inhibitor could be at increased risk of hyperkalemia if spironolactone were introduced (86). RALES may not have shown a significant incidence of hyperkalemia due to the low use of  $\beta$ -blockers, especially considering the potential effects of  $\beta$ -2 receptor antagonism on potassium homeostasis. Despite the “comfort” physicians have with the use of low-dose spironolactone, a decision to routinely use spironolactone, and to do so more frequently than using a  $\beta$ -blocker would appear imprudent. As a result of multiple studies,  $\beta$ -blockers are now known to be effective irrespective of disease severity, while spironolactone has been studied only in patients with more advanced disease.

### Strategies for Clinical Practice

Aldosterone antagonists are undergoing further clinical investigation. Studies will address whether agents that selectively antagonize aldosterone without affecting testosterone are effective, and whether patients with mild disease, those receiving  $\beta$ -blockers, and those with heart failure after a myocardial infarction benefit. In the setting of advanced heart failure, close monitoring of potassium levels is advised even when starting with low doses of spironolactone, and especially with concomitant ACE inhibitor therapy.

### Summary

Compelling clinical trial data mandates that all patients with heart failure receive ACE inhibitors and  $\beta$ -blockers. Therefore, the first step to optimize neurohormonal antagonism in heart failure is to employ ACE inhibitors and  $\beta$ -blockers in all patients who could experience ben-

efit. Without doubt, use of these agents should begin at the time of an acute myocardial infarction and should be started in any patient with ventricular dysfunction who is not volume overloaded or unstable. The HOPE study proves that ACE inhibitors should also be administered to those at risk of cardiovascular events (52). Although no study directly addresses this issue,  $\beta$ -blockers also would appear to be rational therapy for patients at risk, considering the pathophysiology of hypertension, coronary disease and heart failure.

In accordance with this view, the recent AHA/ACC guidelines recommend that diabetic, hypertensive, and hypercholesterolemic patients should be treated with medications in stage A that are safe and effective in stages B, C and D as well. This recommendation means that ACE inhibitors and  $\beta$ -blockers should be used as first line therapy, in particular in those with hypertension or coronary disease. While some may argue that this contradicts the recommendations of the most recent recommendations of the Joint National Commission (JNC-7) (87), the two approaches are quite concordant. JNC-7 recommends diuretics along with a second agent and point out that most patients require 2 or 3 drugs to achieve blood pressure of 130/80 or less (87). If the goal is to minimize risk, then the target blood pressure should be 115/75 or less (88, 89) meaning patients will require at least an ACE inhibitor,  $\beta$ -blocker and diuretic.

Consider the typical 50-year-old. Recent studies using intravascular ultrasound suggest that the likelihood of significant coronary atherosclerosis is at least 75% (90). With such a high likelihood of disease based on age or by applying the Framingham risk calculation, such patients are best managed as if they already have coronary disease. In fact, the medications for preventing cardiac events are the same ones that can control blood pressure, ACE inhibitors and  $\beta$ -blockers. Therefore, the optimal neurohormonal antagonism strategy should not stop with widespread use of ACE inhibitors and  $\beta$ -blockers in patients with symptomatic heart failure, but should be extended to include treatment of those patients at risk of developing heart failure. This is the stage A patient, those with hypertension, coronary artery disease, hypercholesterolemia and/or diabetes.

### Practical Approach

The most rapid and reliable way to improve symptoms in a congested patient is through the judicious use of diuretics. Importantly, patients

who are volume overloaded are not optimal candidates for initiating  $\beta$ -blockers or ACE inhibitors until their volume status has been optimized. When  $\beta$ -blockers are initiated with rapidly increasing doses, the risk of worsening fluid retention is high (50). In contrast, even patients with advanced heart failure tolerate initiation of  $\beta$ -blocker therapy if low starting doses and a gradual up-titration are used, specifically increasing the dose no more frequently than every two weeks (51). In fact, recent data indicates that  $\beta$ -blocker therapy can be initiated at the time of hospitalization, once patients are stabilized, prior to discharge (91). Patients with volume overload and elevated right atrial pressures have a response rate to ACE inhibitors of less than 50% (76), but introduction of these agents in a stabilized patient can be accomplished safely and effectively.

Although ongoing studies appear likely to show an important role for angiotensin receptor blockers, these agents have not been proven beneficial in the studies completed to date, except in patients who are ACE inhibitor intolerant. In contrast, aldosterone antagonism is useful in patients with the advanced disease, but its use requires close monitoring of potassium concentrations for several weeks, especially when used in conjunction with  $\beta$ -blockade and high-dose ACE inhibition.

In clinical practice, the following algorithm should be employed. First, use diuretics to rid the patient of excess volume. This will permit safe and effective introduction of  $\beta$ -blocker and ACE inhibitor therapies. ACE inhibitors can be introduced and increased over the course of 1–2 weeks except in the sickest patients, who will require a more gradual schedule. Within the first 2 weeks of initiation, renal function and electrolytes should be monitored (more frequently in sicker patients and in those with serum creatinine concentrations starting above 1.5 mg/dL). Once the optimal dose has been established and renal function is stable,  $\beta$ -blocker therapy should be started. This titration should be more gradual, and patients should be evaluated at each dose increment. Persistent dizziness can be treated with a temporary reduction in ACE inhibitor or diuretic dose, depending on the clinical scenario, and fluid retention responds to increased diuretic dose that generally permits a continued but more gradual up-titration.

Clinical effects of neurohormonal antagonism include improvements in functional status and ventricular function, but even in the absence of such changes, these agents reduce the

risk of disease progression and death. These are the ultimate targets of optimal neurohormonal antagonism in patients with heart failure and ventricular dysfunction, and can be achieved by widespread use of  $\beta$ -blockers and ACE inhibitors. Available data mandate use of ACE inhibitor therapy in patients at risk of developing heart failure (52), and the clinical practice of using  $\beta$ -blockers earlier in the development of heart failure appears rational.

### Conclusions

Investigators and pharmaceutical companies have focused on the next neurohormonal antagonist, one to complement  $\beta$ -blockers and ACE inhibitors, but have failed. The nature of investigators is to search for the new target and the new therapy, in an effort to change the natural history of disease. Yet the data indicates that the breakthrough treatment for heart failure — and those at risk of developing it — already exists. Neither  $\beta$ -blockers nor ACE inhibitors are prescribed for all eligible patients, and many patients are receiving  $\beta$ -blockers unproven or proven to be inferior, as was demonstrated in COMET (33). Our challenge is to apply the principles of evidence-based medicine, to translate the research findings into clinical practice. Treating patients with stages A, B, C and D heart failure with  $\beta$ -blockers and ACE inhibitors, and where indicated, aldosterone antagonists, is the optimal strategy for neurohormonal antagonism, and by concentrating in particular on the patients with early disease we will have the greatest impact possible on the natural history of the disease.

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