Reviews

Rationale for the Use of Angiotensin II Receptor Blockers in Patients with Left Ventricular Dysfunction (Part I of II)

T. BARRY LEVINE, M.D., AND ARLENE B. LEVINE, M.D.

Division of Cardiology, Allegheny General Hospital, Pittsburgh, Pennsylvania, USA

Summary: Almost 5 million individuals in the United States are diagnosed with chronic heart failure (HF), and the prevalence is increasing. Angiotensin-converting enzyme (ACE) inhibitors and beta blockers, neurohormonal antagonists that block the renin-angiotensin system (RAS) and the sympathetic nervous system, respectively, have been shown in clinical trials to reduce morbidity and mortality in patients with HF, and these therapies are now integral components of standard HF treatment. Yet, morbidity and mortality rates in HF remain unacceptably high, and the limitations of current standard therapies are becoming increasingly apparent. About 10% of patients with HF are unable to tolerate ACE inhibitors, often because of cough. In addition, ACE inhibition may not completely block the RAS because angiotensin II, the main end product of the RAS, can be generated via non-ACE enzymatic pathways. Angiotensin II receptor blockers (ARBs) may exert more complete RAS blockade than ACE inhibitors by interfering with the binding of angiotensin II at the receptor level, regardless of the enzymatic pathway of production. They are also better tolerated than ACE inhibitors and have been shown to improve symptoms and function in clinical trials in patients with HF. These factors provide a strong rationale for the study of the clinical effects of ARBs in patients with HF.

Key words: heart failure, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers

Introduction

Heart failure (HF) remains a major public health problem in the U. S., with increasing prevalence and poor prognosis. Almost 5 million individuals in the U. S. have been diagnosed with HF, and it is estimated that the total direct and indirect

costs for HF in 2004 will reach \$28.8 billion.¹ Although improved treatments appear to extend survival in patients with HF, recent data suggest the associated 1-year and 5-year mortality rates remain approximately 25 and 50%, respectively.^{2,3}

Strongly associated with aging, HF occurs in 6 to 10% of men and women older than 65, who represent 80% of those hospitalized for this disorder.⁴ While other manifestations of cardiovascular disease have declined in prevalence, hospital discharges for HF rose 164%, from 377,000 to 995,000, between 1979 and 2001 (Fig. 1).¹ The prevalence of HF in the U. S. is projected to increase further by two- to three-fold by the year 2010 due to the aging of the population and extended survival of patients with coronary heart disease (CHD).⁵

Treatment of HF has advanced significantly in recent years, based largely on a shift in understanding of the pathophysiology of this disease. Whereas HF was once believed to be essentially a disease of cardiac pump dysfunction, researchers have clarified that HF develops from complex processes of chronic neurohormonal activation and progressive cardiac remodeling.⁶ Substantial clinical trial data have established that neurohormonal antagonists—including angiotensin-converting enzyme (ACE) inhibitors, which suppress the renin-angiotensin system (RAS), and beta blockers, which inhibit sympathetic nervous system (SNS) activation—significantly reduce morbidity and mortality in patients with HF.^{7–12} These therapies are now widely recommended as first-line therapies in HF management.^{4,13} The utilization of ACE inhibitors in clinical practice, however, may be limited by associated adverse effects, particularly cough, and incomplete long-term blockade of the RAS due to the formation of angiotensin II by non-ACE enzymatic pathways.^{14,15} In fact, prognosis of HF remains poor despite utilization of ACE inhibitors and beta blockers.^{1–3} Angiotensin II receptor blockers (ARBs) also inhibit the RAS and are generally better tolerated than ACE inhibitors.¹⁶ Furthermore, ARBs may provide more complete blockade of the RAS at the receptor level, independent of the pathway of angiotensin II generation.¹⁶ These factors suggest that ARBs may provide significant clinical benefits in patients with chronic HF, either when used in ACE inhibitor-intolerant patients or when added to ACE inhibitor therapy.¹⁷

Pathogenesis of Heart Failure: Overview

Heart failure develops due to progressive cardiac remodeling, which involves programmed cell death or apoptosis, dis-

Address for reprints:

T. Barry Levine, M.D.
Director, Division of Cardiology
Allegheny General Hospital
320 East North Avenue
Pittsburgh, PA 15212-4772, USA
e-mail: blevine@wpahs.org

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FIG. 1 Hospital discharges for heart failure (HF) between 1979 and 2001. Adapted from Ref. No. 1.

solution of the collagen that holds the myocytes together (myocyte slippage), hypertrophy of cardiac myocytes, and growth of interstitial matrix.⁶ This leads to impaired ability of the left ventricle to pump blood (systolic HF) and/or fill with blood (diastolic HF), causing insufficient tissue perfusion and resulting in the typical signs and symptoms of HF—progressive dyspnea, fatigue, and fluid retention or edema—on which the New York Heart Association Class I-IV staging system for HF is based.¹⁸ Approximately 35 to 50% of HF cases occur in the face of preserved systolic function, that is, diastolic HF.¹⁹

Hypertension is the most common risk factor for both systolic and diastolic HF, preceding HF in 91% of cases.²⁰ Long-term hypertension causes pressure overload of the left ventricle (Fig. 2).^{6,21} The resulting left ventricular (LV) hypertrophy and accompanying LV wall stiffness can lead to abnormal LV filling and diastolic HF (Fig. 2).⁶ Hypertension is also a major risk factor for the development of CHD and myocardial infarction, resulting in progressive LV remodeling and dysfunction, and systolic HF (Fig. 2).⁶

Left ventricular dysfunction and reduced tissue perfusion trigger increased neurohormonal activation, including renin release and adrenergic drive, as compensatory responses to support heart rate and myocardial contractility.^{6,22} In an enzymatic cascade, renin cleaves angiotensinogen to release angiotensin I, which is then converted, primarily by ACE, into angiotensin II, the main end product and effector of the RAS. Angiotensin II is a powerful vasoconstrictor that affects SNS activation, blood pressure control, and natriuresis, among other biologic functions.²³ While neurohormonal activations may provide short-term support of cardiac function in the patient with HF, they contribute long-term to progressive LV remodeling and dysfunction.⁶ Increased neurohormonal activation has been shown to be a significant predictor of cardiovascular mortality in patients with asymptomatic LV dysfunction.²²

Major Goals of Heart Failure Management

The American College of Cardiology and American Heart Association have jointly developed a system for staging and

FIG. 2 Progression to heart failure (HF). LVH = left ventricular hypertrophy, MI = myocardial infarction, LV = left ventricle. Reprinted from Ref. No. 21 with permission.

management of HF, based on the neurohormonal model of progressive LV remodeling (Fig. 3).⁴ The two primary goals of HF treatment are (1) to relieve symptoms and improve quality of life, and (2) to slow or reverse the long-term progression of the disorder, and thereby prolong survival (Fig. 3).^{4,24} Restriction of salt intake, exercise, and treatment with loop diuretics and digoxin are the standard therapies to relieve symptoms by reducing circulatory congestion and by increasing tissue perfusion.^{4,13}

The main therapies recommended to slow, or even reverse, HF progression are ACE inhibitors, which block the RAS, and beta blockers, which inhibit the SNS (Fig. 3).^{4,13} Long-term neurohormonal suppression with these therapies reduces mortality in patients with chronic HF through inhibition of cardiac remodeling and improvement of LV structure and function.^{25–27}

The clinical benefits of ACE inhibitors and beta blockers in HF are well supported by large-scale clinical trials. In the landmark Studies of Left Ventricular Dysfunction (SOLVD) trial in

FIG. 3 American College of Cardiology/American Heart Association algorithm for treatment of heart failure (HF). ACE = angiotensin converting enzyme. Adapted from Ref. No. 4.

patients with systolic HF ($n = 2,569$), enalapril was associated with reductions of 16% in all-cause mortality ($p = 0.0036$) and 18% in cardiovascular disease mortality ($p < 0.002$), compared with placebo, after an average follow-up of 3.5 years.⁸ Moreover, several large-scale clinical trials have consistently demonstrated reductions in overall mortality of approximately 35% with the addition of beta blockers to other standard HF therapies, including ACE inhibitors, diuretics, and digoxin.^{10–12}

Finally, the aldosterone inhibitor spironolactone has been shown to reduce morbidity and mortality in patients with severe HF when added to conventional therapy.²⁸ Spironolactone should therefore be considered part of the standard therapeutic regimen in patients with advanced HF.

Rationale for Angiotensin II Receptor Blockers in the Management of Heart Failure

Use of ACE inhibitors suppresses the formation of angiotensin II. However, this mechanism of action may not provide optimal long-term RAS blockade since there are alternate, non-ACE pathways of angiotensin II formation. Angiotensinogen can be converted to angiotensin II by non-renin enzymes, including tissue plasminogen activator (t-PA), cathepsin G, elastase, and chymostatin, while angiotensin I can be converted to angiotensin II by non-ACE enzymes such as chymostatin-sensitive angiotensin II-generating enzyme, chymase, and cathepsin G.²³ Studies have in fact demonstrated “angiotensin II escape,” with return of angiotensin II to pretreatment levels, during chronic ACE inhibitor therapy.^{15, 29–31} Rebound of angiotensin II levels during ACE inhibitor therapy has been correlated with excess mortality in patients with HF.¹⁵ In addition, ACE inhibition is associated with persistent cough in up to 20% of patients, and angioedema in 0.1 to 0.2% of patients.¹⁴ In the Omapatrilat Cardiovascular Treatment vs. Enalapril (OCTAVE) trial, the frequency of angioedema with enalapril was 0.68% (86 of 12,557 patients with hyperten-

sion), and was 1.62% in black patients.³² The Study of Patients Intolerant of Converting Enzyme Inhibitors (SPICE) Registry found that approximately 9% of patients with systolic HF were not receiving ACE inhibitors due to prior intolerance.³³ These adverse events may be due to the accumulation of bradykinins associated with ACE inhibitor therapy.³⁴ On the other hand, the potential contribution of bradykinin-mediated effects to the benefits of ACE inhibitors on clinical outcomes has not been established.

Angiotensin II binds with highly specific receptors on the cell membrane to exert its effects. The two major subtypes of angiotensin II receptors identified in humans are the angiotensin II type 1 (AT₁) and the angiotensin II type 2 (AT₂). The AT₁ receptor is responsible for mediating virtually all of the pathologic effects of angiotensin II, such as vasoconstriction and cellular proliferation and hypertrophy (Table I).^{16, 23} Although the function of the AT₂ receptor is less well understood, some evidence suggests this receptor may mediate processes such as vasodilation and cell apoptosis that oppose the effects of the AT₁ receptor (Table I).^{23, 35}

The ARBs selectively inhibit the binding of angiotensin II to the AT₁ receptor, regardless of the enzymatic pathway of angiotensin II formation.¹⁶ They also allow the binding of angiotensin II to the AT₂ receptors, further counteracting the pathogenic effects of angiotensin II.²³ This mechanism of action provides a more specific and complete blockade of the deleterious effects of angiotensin II than does ACE inhibition alone. In addition, ARBs do not result in accumulation of bradykinins, and thus have a considerably lower risk of cough and angioedema than ACE inhibitors.³⁴ Indeed, ARBs have generally demonstrated tolerability similar to that of placebo in hypertension clinical trials.¹⁶ These factors have stirred considerable interest in the potential clinical benefits of ARBs in the management of chronic HF.¹⁷ These two classes of agents thus provide important inhibition of the RAS via different mechanisms of action and may be clinically useful, either alone or in combination, in the management of chronic HF.

TABLE I AT₁ and AT₂ receptor-mediated activities

AT ₁ receptor	AT ₂ receptor
Vasoconstriction	Vasodilation
Vascular smooth muscle cell proliferation	Inhibition of cell growth/proliferation
Extracellular matrix formation	Modulation of extracellular matrix
Aldosterone synthesis and secretion	Fetal tissue development
Renal tubular sodium reabsorption	Stimulation of apoptosis
Increased vasopressin secretion	Neuronal regeneration
Decreased renal blood flow	Cell differentiation
Renal renin inhibition	
Cardiac hypertrophy	
Cardiac contractility	
Augmentation of peripheral nonadrenergic activity	
Modulation of central sympathetic nervous system activity	
Central osmocontrol	

Abbreviations: AT₁ = angiotensin II type 1, AT₂ = angiotensin II type 2.

Adapted from Ref. No. 23.

Conclusion

The persistently high morbidity and mortality rates among patients with HF indicate that additional therapeutic options are needed. While ACE inhibitors significantly reduce HF morbidity and mortality, they may provide incomplete long-term blockade of the RAS and are poorly tolerated in up to 10% of patients with HF. Angiotensin II receptor blockers are generally better tolerated than ACE inhibitors and may provide more complete inhibition of the RAS. Thus, there is a compelling rationale for investigating the clinical effects of ARBs among patients with HF.

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