

Combination Therapy with ACE Inhibitors and Angiotensin-Receptor Blockers in Heart Failure

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Angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers have different pharmacologic mechanisms for blocking the effect of the renin-angiotensin-aldosterone system on the cardiovascular system. Pharmacologically, the combination of these drug classes completely blocks the deleterious effect of angiotensin in patients with heart failure. However, clinical trials have not shown a marked benefit from using this combination compared with using angiotensin-converting enzyme inhibitors alone. Patients who take combination therapy do not live longer, although they are less likely to be hospitalized for worsening symptoms. Most patients who take combination therapy will not experience marked improvement in symptoms or quality of life. (Am Fam Physician 2003;68:1795-8. Copyright© 2003 American Academy of Family Physicians.)

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Despite recent advances in treatment, heart failure carries a high risk of morbidity and mortality. About 550,000 new cases are diagnosed annually, and approximately 50,000 persons die of heart failure each year.¹

The treatment goal in patients with heart failure is twofold: to control symptoms and to extend life span. Beta blockers,² angiotensin-converting enzyme (ACE) inhibitors,³ and spironolactone (Aldactone)⁴ have been shown to decrease mortality. Angiotensin-receptor blockers also have been studied in the treatment of heart failure, and several studies have shown significant symptomatic improvement, similar to that associated with ACE inhibitor therapy. However, angiotensin-receptor blockers do not decrease mortality rates in patients with heart failure.⁵

Because of their different mechanisms of action, ACE inhibitors and angiotensin-receptor blockers are not interchangeable. However, when used in combination, they theoretically may benefit patients with heart failure. This article reviews the literature and available evidence on the use of ACE inhibitors and angiotensin-receptor blockers in combination for the treatment of patients with congestive heart failure.

Pathophysiology

The renin-angiotensin-aldosterone system plays an important role in the development and progression of cardiovascular disease. ACE inhibitors and angiotensin-receptor blockers affect the system at different levels and thus may have an additive effect. Angiotensinogen, the initial substrate of the renin-angiotensin-aldosterone system, is produced in the liver; renin converts it to angiotensin I in the kidneys. ACE converts angiotensin I to angiotensin II, a potent vasoconstrictor with a broad spectrum of activity in target organs. Angiotensin II also stimulates the release of aldosterone, which causes sodium and fluid retention. The actions of angiotensin II are mediated by receptor AT₁, which triggers detrimental effects, and AT₂, which triggers some beneficial effects.

Another component of the renin-angiotensin-aldosterone system is bradykinin, a vasoactive peptide metabolized by the same enzyme that converts angiotensin I to angiotensin II. The use of ACE inhibitors to block the breakdown of bradykinin also promotes vasodilation, natriuresis, and a beneficial effect on cardiac remodeling.

Studies have shown that despite adequate

See page 1692 for definitions of strength-of-evidence levels.

ACE inhibition, angiotensin II levels eventually return to nearly normal levels, because the chymase enzymes are an alternate pathway for angiotensin conversion. Angiotensin-receptor blockers work by blocking the effects of angiotensin II at the AT₁ receptor, allowing beneficial effects at the AT₂ receptor. When angiotensin-receptor blockers are taken alone, the inactivation of bradykinin proceeds normally, without the beneficial accumulation promoted by ACE inhibitors. The use of an ACE inhibitor in combination with an angiotensin-receptor blocker theoretically could offer benefits by allowing bradykinin to accumulate while blocking the deleterious consequences of angiotensin II.

Search Methods

To find relevant patient-oriented research, we searched MEDLINE, InfoRetriever, and our own files for “angiotensin-receptor blockers” and “ARBs.” We limited the research to randomized controlled trials (RCTs) that evaluated the role of angiotensin-receptor blockers and ACE inhibitors on patient-oriented outcomes.

Our literature review found a small number of studies that dealt specifically with the combination of ACE inhibitors and angiotensin-receptor blockers. Most of the

early studies were of short duration and had few participants. Many of the studies focused solely on the physiologic effects of therapy.

MORTALITY

Based on a meta-analysis of six studies involving nearly 6,000 patients, the addition of an angiotensin-receptor blocker to ACE inhibitor therapy is not more effective than ACE inhibitor treatment alone in reducing mortality.⁵ [Evidence level A, meta-analysis] The largest study was the Valsartan Heart Failure Trial (Val-HeFT),⁶ a randomized, placebo-controlled trial involving 5,010 patients over nearly two years.

Patients in Val-HeFT⁶ had an ejection fraction of less than 40 percent and a New York Heart Association (NYHA) classification of II to IV. Patients took an ACE inhibitor (92 percent) and/or diuretic (85 percent), and some patients also took digoxin and beta blockers. In addition to this “background therapy,” patients received valsartan, in a dosage of 40 mg twice daily, titrated to 160 mg twice daily, or placebo. During the two-year follow-up period, 19 percent of study participants died; there was no difference in mortality rates between the angiotensin-receptor-blocker group and the placebo group (relative risk [RR], 1.02; 95 percent confidence interval [CI], 0.90 to 1.15).

A recently published study, the Candesartan in Heart Failure: Assessment of Mortality and Morbidity (CHARM)-Added study,⁷ has shown similar results. In this study, 2,548 patients with a NYHA classification of II to IV who already were taking an ACE inhibitor were randomized to receive placebo or candesartan up to 32 mg daily. As with the Val-HeFT trial and the meta-analysis, overall death rates were similar with and without candesartan.

HOSPITALIZATION

Angiotensin-receptor blockers, used in combination with ACE inhibitors, decrease the hospitalization rate in patients with heart failure. A meta-analysis of three studies with nearly 6,000 patients found a reduction in hospitalization rates in patients who took the combination of an ACE inhibitor and an angiotensin-receptor blocker, compared with patients who took an ACE inhibitor alone (RR, 0.74; 95 percent CI, 0.64 to 0.86).^{5,6} [Reference 6—Evidence level A, RCT] Patients in the Val-HeFT and CHARM-Added studies had similar results. Compared with ACE inhibitor treatment alone, one hospitalization is prevented for every 21 patients treated with the combina-

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tion of an ACE inhibitor and an angiotensin-receptor blocker for two years.⁵

SYMPTOMS

When added to ACE inhibitor therapy, angiotensin-receptor blockers have little effect on exercise capacity, functional capacity, and quality of life. A number of studies have evaluated the effect of adding angiotensin-receptor blockers to ACE inhibitors to control symptoms of heart failure. In many of these studies, the end points were physiologic events such as plasma norepinephrine levels, aldosterone levels, end systolic/diastolic volumes, and peak exercise capacity. However, more important outcomes are measures of exercise capacity, functional capacity (using the NYHA classification), and quality of life.

One randomized, double-blind, placebo-controlled study⁸ of 20 patients over 12 weeks found that the combination of an ACE inhibitor and an angiotensin-receptor blocker was well tolerated, but that patients taking the combination had no significant improvement in exercise capacity, quality of life, or physiologic measurements of hemodynamics or neurohormones. Although this was a small study, it was large enough to have found a significant change (i.e., more than 25 percent) in exercise capacity if such a change had been present. Another study⁹ evaluating exercise toler-

The addition of an angiotensin-receptor blocker to angiotensin-converting enzyme (ACE) inhibitor therapy is not more effective than ACE inhibitor treatment alone in reducing mortality.

ance time found no difference after 12 weeks of combined therapy compared with an ACE inhibitor alone, although this study probably was underpowered.

A longer study¹⁰ found a significant reduction of symptoms in patients who received combination therapy. In 33 patients treated with the combination for six months, exercise capacity as measured by peak aerobic capacity (maximal oxygen consumption [VO₂]) improved significantly. Functional capacity also improved, with nine of 16 patients (56 percent) in the combination group improving by one NYHA class, compared with one of 17 patients (6 percent) treated with an ACE inhibitor plus placebo.

In contrast, two larger studies of the angiotensin-receptor blockers valsartan⁶ and candesartan¹¹ found little effect on symptoms in patients receiving combination therapy compared with patients receiving conventional therapy that included an ACE inhibitor. In the candesartan study,¹¹ 768

TABLE 1
Effects of Drugs Used in the Treatment of Heart Failure

<i>Medications</i>	<i>Morbidity rate</i>	<i>Hospitalization rate</i>	<i>Mortality rate</i>
ACE inhibitors	Decrease	Decrease	Decrease
Beta blockers	Decrease	Decrease	Decrease
Spironolactone (Aldactone)	Insufficient evidence	Insufficient evidence	Decrease
Hydralazine (Apresoline) and isosorbide dinitrate (Isordil)	Insufficient evidence	No benefit	Decrease
Angiotensin-receptor blockers	Decrease	Insufficient evidence	Insufficient evidence
Diuretics	Decrease	Insufficient evidence	Insufficient evidence
Digoxin	Decrease	Decrease	No benefit
ACE and angiotensin-receptor blocker combination	Insufficient evidence	Decrease	No benefit
ACE inhibitor, angiotensin-receptor blocker, and beta blocker combination	Insufficient evidence	Insufficient evidence	Insufficient evidence

ACE = angiotensin-converting enzyme.

Information from reference 12.

Angiotensin-receptor blockers, used in combination with angiotensin-converting enzyme inhibitors, decrease the hospitalization rate in patients with heart failure.

patients received candesartan or enalapril (Vasotec) alone or the two drugs in combination. Investigators found no difference in exercise capacity (as measured by six-minute walking distance), quality of life (as measured by the Minnesota Living with Heart Failure Questionnaire), or NYHA functional class. In the valsartan study,⁶ there was a statistically significant improvement in symptoms when an angiotensin-receptor blocker was added to standard therapy that included an ACE inhibitor, although both groups had similar improvements in NYHA classification (23.1 percent versus 20.7 percent, $P = .001$) and percentage of patients whose classification declined (10.1 percent versus 12.8 percent, $P < .001$). Quality of life was not affected by the addition of valsartan.

Discussion

Several options exist for delaying mortality and reducing hospitalizations and symptoms in patients with congestive heart failure (see accompanying table).¹² In addition to digoxin and a diuretic (one or more doses per day) to treat symptoms, patients also could be treated with an ACE inhibitor, a beta blocker, an angiotensin-receptor blocker, spironolactone, or aspirin. The law of diminishing returns applies to these treatments—the incremental benefit of additional therapy decreases with each medication added. Such is the case with the angiotensin-receptor blockers.

There are two approaches to determining the effectiveness of angiotensin-receptor blockers in combination with ACE inhibitors. One approach is to assume a “class effect” (meaning that there is no difference among the angiotensin-receptor blockers); thus, the results of trials of different agents can be combined. The other approach is to acknowledge a potential difference in pharmacology among the angiotensin-receptor blockers and to compare one agent in the class with another.¹³ However, no convincing evidence shows that these mechanistic differences have a major clinical effect; more importantly, no comparative studies of angiotensin-receptor blockers have been published.

In terms of morbidity and mortality, ACE inhibitors and beta blockers have well-established, substantial benefits in

the treatment of congestive heart failure. Although some patients taking combination therapy will be hospitalized less often than patients taking an ACE inhibitor alone, the majority of patients will not live longer or better with combination therapy.

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REFERENCES

1. American Heart Association. Heart disease and stroke statistics—2002 update. Dallas: American Heart Association, 2001.
2. Lechat P, Packer M, Chalon S, Cucherat M, Arab T, Boissel JP. Clinical effects of beta-adrenergic blockade in chronic heart failure: a meta-analysis of double-blind, placebo-controlled, randomized trials. *Circulation* 1998;98:1184-91.
3. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. *N Engl J Med* 1987;316:1429-35.
4. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999;341:709-17.
5. Jong P, Demers C, McKelvie RS, Liu PP. Angiotensin receptor blockers in heart failure: meta-analysis of randomized controlled trials. *J Am Coll Cardiol* 2002;39:463-70.
6. Cohn JN, Tognoni G, Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001;345:1667-75.
7. McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, et al; CHARM investigators and committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet* 2003;362:767-71.
8. Houghton AR, Harrison M, Cowley AJ, Hampton JR. Combined treatment with losartan and an ACE inhibitor in mild to moderate heart failure: results of a double-blind, randomized, placebo-controlled trial. *Am Heart J* 2000;140:791-6.
9. Tonkon M, Awan N, Niazi I, Hanley P, Baruch L, Wolf RA, et al. A study of the efficacy and safety of irbesartan in combination with conventional therapy, including ACE inhibitors, in heart failure. Irbesartan Heart Failure Group. *Int J Clin Pract* 2000;54:11-4,16-8.
10. Hamroff G, Katz SD, Mancini D, Blaufarb I, Bijou R, Patel R, et al. Addition of angiotensin II receptor blockade to maximal angiotensin-converting enzyme inhibition improves exercise capacity in patients with severe congestive heart failure. *Circulation* 1999;99:990-2.
11. McKelvie RS, Yusuf S, Pericak D, Avezum A, Burns RJ, Probstfield J, et al. Comparison of candesartan, enalapril, and their combination in congestive heart failure: randomized evaluation of strategies for left ventricular dysfunction (RESOLVD) pilot study. The RESOLVD Pilot Study Investigators. *Circulation* 1999;100:1056-64.
12. Margo KL, Luttermoser G, Shaughnessy AF. Spironolactone in left-sided heart failure: how does it fit in? *Am Fam Physician* 2001;64:1393-8.
13. Willenheimer R, Dahlof B, Rydberg E, Erhardt L. AT1-receptor blockers in hypertension and heart failure: clinical experience and future directions. *Eur Heart J* 1999;20:997-1008.