CME CREDIT

ONE MINUTE CONSULT

BRIEF QUESTIONS AND ANSWERS ON CURRENT CLINICAL CONTROVERSIES

Q: Is there an advantage to combination therapy with ACE inhibitors and angiotensin II-receptor blockers?

DONALD G. VIDT, MD

Senior physician, Department of Nephrology and Hypertension, Cleveland Clinic; Professor of Internal Medicine, Ohio State University; member, Sixth Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure

A: Although we have some preliminary evidence from small studies that there is an advantage to using angiotensin-converting enzyme (ACE) inhibitors and angiotensin II-receptor blockers (ARBs) in combination, this advantage needs to be confirmed in larger trials before a definitive statement can be made.

HARMFUL EFFECTS OF ANGIOTENSIN II

The hormone angiotensin II has a multitude of effects in the body, binding to receptors in the heart, kidneys, gonads, placenta, pituitary gland, adrenal glands, peripheral vessels, and central nervous system.[1] As a vasopressor, it raises blood pressure and decreases blood flow to the kidneys, decreasing fluid excretion. In addition, it stimulates aldosterone production, which promotes retention of sodium and bicarbonate and excretion of potassium and hydrogen, leading to more fluid retention and hypertension. It also contributes to causing proteinuria,[2] an independent risk factor for progressive renal disease. Moreover, it induces cell hyperplasia, leading to hypertrophy of the arteries and arterioles and left ventricular hypertrophy in the heart.

BENEFITS OF ACE INHIBITORS

When ACE inhibitors became available in the early 1980s, they were a tremendous advance. Studies show that these drugs:

- Lower blood pressure at least as well as other classes of antihypertensive agents.
- Reduce urinary protein excretion and slow the loss of renal function in hypertensive patients with diabetic or nondiabetic progressive renal disease. The effects are greater than with other antihypertensive drugs that lower the blood pressure by a comparable amount.
- Reduce the rates of mortality and hospitalization in patients with heart failure.
- Cause regression of left ventricular hypertrophy.
- Have a cardioprotective effect in patients surviving an acute myocardial infarction.
- May prevent myocardial infarctions, strokes, and deaths from cardiovascular causes in patients with coronary artery disease, previous stroke, or peripheral vascular disease, as shown in the recent Heart Outcomes Prevention Evaluation (HOPE) study.[3]

BENEFITS OF ARBs

The ARBs, a newer class of drugs, act lower in the angiotensin cascade than do ACE inhibitors (FIGURE 1). No large-scale clinical trials have yet compared ACE inhibitors vs ARBs in patients with specific cardiovascular or renal diseases, but preliminary studies in animals and humans suggest that, like ACE inhibitors, ARBs:

- Reduce proteinuria and slow loss of renal function in both diabetic and nondiabetic renal disease.
- Induce regression of left ventricular hypertrophy.
- Reduce morbidity and mortality and improve functional performance in patients with congestive heart failure.

Several large clinical trials are underway to confirm these findings. At present, many physicians use ARBs as alternatives to ACE

Preliminary data suggest that combination therapy may be beneficial

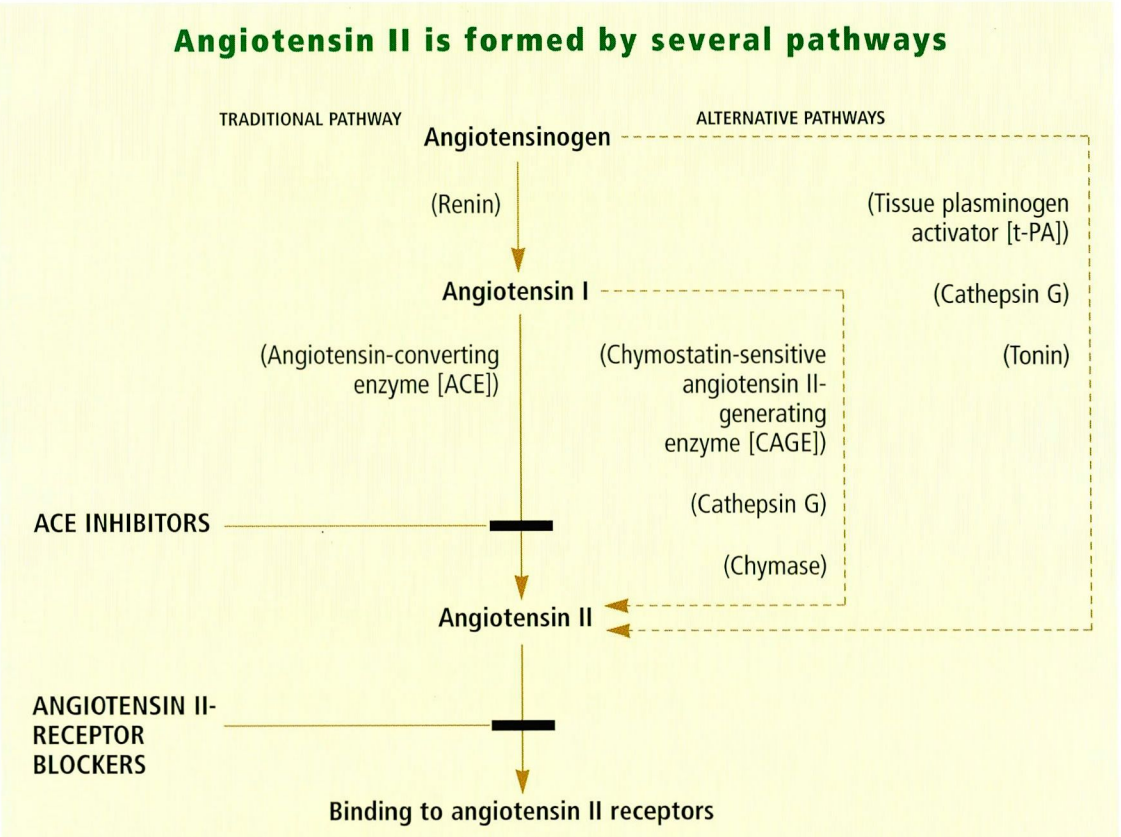

FIGURE 1. Pathways for formation of angiotensin II. The clinical significance of alternative pathways, ie, those that are not blocked by ACE inhibitors, is not known.

ADAPTED FROM DZAU VJ. MULTIPLE PATHWAYS OF ANGIOTENSIN PRODUCTION IN THE BLOOD VESSEL WALL: EVIDENCE, POSSIBILITIES AND HYPOTHESES. J HYPERTENS 1989; 7:933–936.

In theory, combination therapy should block the renin-angiotensin system more completely

inhibitors for patients with heart failure who cannot tolerate ACE inhibitors, although no ARB as yet is approved for this indication.

THEORETIC ADVANTAGES OF COMBINATION THERAPY

In theory, the combination of ARBs and ACE inhibitors may be beneficial for two reasons.

ACE inhibitors do not completely inhibit angiotensin II generation, because alternative pathways exist for producing this hormone (FIGURE 1). The combination of an ACE inhibitor and an ARB should block the renin-angiotensin system more completely.

In addition, ACE inhibitors prevent the breakdown of bradykinin and vasodilator prostaglandins. Recent studies in rats suggest that increased kinin activity contributes to the antiproteinuric and antihypertensive effects of ACE inhibitors.[4,5] In contrast, ARBs have no effect on these substances.

PRELIMINARY DATA WITH COMBINATION THERAPY

Study in normal volunteers

A crossover study in 12 mildly sodium-depleted normotensive subjects[6] showed that the combination of losartan (an ARB) and captopril (an ACE inhibitor) decreased the blood pressure and increased plasma renin levels more than did either agent used alone.

Studies in patients with heart failure

In an open study,[7] 43 patients with congestive heart failure who were already receiving recommended doses of ACE inhibitors (or the highest dose they could tolerate) were also given losartan 25 mg/day for one week and then 50 mg/day for another week. The mean systolic blood pressure decreased from 122 mm Hg at baseline to 107 mm Hg at 2 weeks. The decrease was well tolerated, even in patients who had symptomatic hypotension during up-titration of the ACE inhibitor.

In a randomized study,[8] 33 patients with severe congestive heart failure who were already receiving maximal doses of ACE inhibitors were randomly assigned to also receive either losartan 50 mg/day or placebo. At 6 months, exercise capacity had increased and functional class had remained the same in patients receiving combination therapy, whereas both had declined in those receiving ACE inhibitors alone. The combination was well tolerated.

In the pilot phase of the International Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) trial, patients were randomized to receive an ARB, an ACE inhibitor, or combination therapy.[9] The ARB had an effect similar to the ACE inhibitor on functional capacity, ventricular function, blood pressure, suppression of aldosterone, and other neurohormones except for angiotensin II. The combination of the two drugs suppressed aldosterone levels to a greater extent in both the short term and the long term, increased the left ventricular ejection fraction, and decreased ventricular volumes substantially, resulting in a greater reduction in blood pressure. Combination therapy also appeared to be more effective in preventing cardiac remodeling. This study was too small to detect differences in clinical events, but a much larger study is underway.

The Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) study will randomize three patient groups to an ARB or placebo: those with decreased systolic function who are taking an ACE inhibitor, those with decreased systolic function who are ACE inhibitor-intolerant, and those with normal ejection fractions not taking ACE inhibitors.

Studies in patients with renal disease

In a study in seven patients with diabetic nephropathy who were already taking ACE inhibitors,[10] the addition of losartan 25 or 50 mg resulted in an increase in plasma renin levels but no change in urinary protein.

In eight normotensive patients with IgA nephropathy,[11] the combination of an ACE inhibitor and an ARB decreased proteinuria more than either drug alone.

Long-term studies are necessary to confirm the additive effects of combined therapy on functional capacity of specific target organs, quality of life, and survival.

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Exercise capacity increased with combination therapy