

FROM THE FAMILY PRACTICE INQUIRIES NETWORK

Is combining ACE inhibitors and ARBs helpful or harmful?

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■ EVIDENCE-BASED ANSWER

The combination of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) has been studied for treatment of heart failure, hypertension, and proteinuric renal disease. Combination therapy with an ACE inhibitor and an ARB decreases symptoms in heart failure patients, but does not appear to have an impact on overall mortality (strength of recommendation [SOR]: **A**).

Preliminary data from small trials indicate that combination therapy may be more effective than monotherapy with an ACE inhibitor or an ARB for lowering blood pressure (SOR: **B**), although morbidity and mortality data for the combination are not currently available. Additionally, in trials involving diabetic and nondiabetic proteinuric renal disease, the combination of ACE inhibitors and ARBs delays progression of renal disease to a greater extent than monotherapy; however, mortality data are also unavailable (SOR: **A**).

■ EVIDENCE SUMMARY

ACE inhibitors have been used most commonly for the treatment of congestive heart failure and hypertension and to slow the progression of proteinuria. Their primary mechanism of action is the suppression of angiotensin II by blocking its formation via renin and angiotensin I, thereby reducing the main deleterious effects of angiotensin II, which are mediated through vaso-constriction. Other pathways of angiotensin II formation exist and may escape inhibition of the converting enzyme.¹ ARBs block the action of angiotensin II at the AT1 receptor and may, in theory, provide additive benefit.

The data describing the use of the combination of an ACE inhibitor and an ARB in heart failure are from the Valsartan Heart Failure Trial (ValHeFT),² the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity Trial (CHARM),³ and in the Valsartan in Acute Myocardial Infarction Trial (VALIANT).⁴

In ValHeFT, 5010 patients with systolic dysfunction were randomized to the ARB valsartan or placebo in

addition to background therapy, which included an ACE inhibitor in 93% of subjects. The primary endpoints were mortality and combined mortality and morbidity. An increase in mortality was found among patients on the triple therapy combination of valsartan, an ACE inhibitor, and a beta-blocker (relative risk [RR]=1.4; 95% confidence interval [CI], 1.1–1.9). Among those not on beta-blockers, adding valsartan to baseline therapy of an ACE inhibitor resulted in a modest improvement in the combined endpoint (RR=0.8; 95% CI, 0.7–0.9), but no change in mortality alone was found.²

In CHARM, candesartan was added to baseline therapy among patients with heart failure. Baseline therapy included diuretics (90%), beta blockers (55%), spironolactone (17%), and other cardiovascular medications as necessary. In this study, those in the treatment arm had a decrease in the combined endpoint of cardiovascular death plus congestive heart failure admission (RR=0.85; 95% CI, 0.75–0.96), but no difference was seen in overall mortality. Of note, no adverse interaction was demonstrated for those on the triple combination of ACE inhibitors, ARBs, and beta-blockers.³

Similarly, VALIANT demonstrated the safety but the lack of incremental efficacy in adding valsartan to ACE inhibitors for patients with left ventricular dysfunction after a myocardial infarction.⁴

Limited evidence is available from randomized controlled trials on the safety or efficacy of combination therapy exclusively for hypertensive patients. The available published trials were short-term and assessed blood pressure rather than more clinically significant endpoints such as risk of cardiovascular events and mortality. One trial of 177 patients found no significant difference in 24-hour ambulatory mean diastolic blood pressure with combination therapy vs ACE inhibitor or ARB monotherapy, but did show a decrease in clinic diastolic blood pressure.⁵ Another small trial of 20 patients demonstrated improved ambulatory blood pressure control with combination therapy vs ACE inhibitor monotherapy.⁶

Several trials have investigated the effect of combination therapy on diabetic and nondiabetic proteinuria. Conclusions from these trials are limited by their small sample size and by measurement of intermediate outcomes without mortality data. The largest trial, COOPERATE, was conducted in Japan and included 336 patients with nondiabetic renal disease.⁷ The investigators found that significantly fewer patients receiving combination therapy reached the combined primary endpoint of time to doubling of serum creatinine or end-stage renal disease compared with patients receiving monotherapy. The CALM study included 199 patients with hypertension, micro-albuminuria, and type 2 diabetes mellitus, and demonstrated significantly greater attenuation of urinary albumin/creatinine ratio and significantly improved blood pressure control with combination therapy compared with either therapy alone.⁸

Another trial, ONTARGET, is being conducted to assess the impact of ACE inhibitor or ARB monotherapy and combination therapy on reducing cardiovascular risk; it includes a combined primary endpoint of morbidity and mortality. The study involves 23,400 high-risk patients and will have a follow-up period of 5.5 years. This trial enrolls patients who have coronary disease, cerebrovascular disease, peripheral vascular disease, or diabetes with end-organ damage (inclusion and exclusion criteria are based upon those used in the HOPE study).

■ RECOMMENDATIONS FROM OTHERS

We were unable to find to find any recommendations regarding the addition of ARB drugs to ACE inhibitors.

CLINICAL COMMENTARY

Adding ARBs to ACE inhibitors: Good in theory, but clinical evidence is still weak

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There is good evidence of the benefits of angiotensin inhibition in multiple diseases, so it is logical to ask if adding receptor blockers adds further benefit. For now, it appears that the addition of an ARB to an ACE inhibitor is an idea that sounds good in theory, but needs more data to prove its clinical benefit and safety.

The clinical evidence for the combo in heart failure and hypertension is weak, since mortality data are lacking and there is the troubling association with increased mortality in the presence of beta blockers. Using the combination is not currently recommended by the major national guidelines for those areas (eg, American Heart Association, Joint National Committee VII). Although the benefit for patients with proteinuria appears promising, we still await evidence for decreasing mortality. Given cost and the combination's uncertain benefit, it would be prudent to wait until the completion of studies currently in progress before we embrace it.

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