

# FPIN's Help Desk Answers

## Pharmacologic Therapy for Heart Failure

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### Clinical Question

Should physicians use a combination of an angiotensin-converting enzyme (ACE) inhibitor and an angiotensin receptor blocker (ARB) in patients with heart failure?

### Evidence-Based Answer

Compared with monotherapy, the combination of an ACE inhibitor and an ARB has not been shown to improve cardiovascular or overall mortality in patients with symptomatic heart failure. The combination is associated with an increased number of adverse drug effects. (Strength of Recommendation [SOR]: A, based on a meta-analysis and randomized controlled trial [RCT].)

### Evidence Summary

A 2012 meta-analysis of 24 RCTs evaluated the use of ARBs in patients who had symptomatic heart failure with left ventricular systolic dysfunction (left ventricular ejection fraction [LVEF] 40% or less) and preserved ejection fraction (LVEF greater than 40%).<sup>1</sup> The meta-analysis included studies comparing ARBs vs. placebo, ARBs vs. ACE inhibitors, or ACE inhibitors plus ARBs vs. ACE inhibitors alone. The dual vs. monotherapy comparison comprised 8,260 patients (20% women) with a mean age of 63 years (range: 60 to 66 years) and a mean LVEF of 27% (range: 20% to 29%). Primary outcomes

included total mortality (cardiovascular and noncardiovascular), cardiovascular morbidity (myocardial infarction, stroke), total hospitalizations, and withdrawal due to adverse drug effects. There was no difference in total mortality (seven studies; n = 8,260; relative risk [RR] = 0.98; 95% CI, 0.90 to 1.06) or cardiovascular mortality (two studies; n = 7,558; RR = 0.93; 95% CI, 0.84 to 1.03) between the groups. There was a significant decrease in the number of myocardial infarctions in the combination therapy group (one study; n = 2,548; RR = 0.64; 95% CI, 0.44 to 0.92) and a decrease in the risk of hospitalization for heart failure (two studies; n = 2,989; RR = 0.81; 95% CI, 0.74 to 0.89). Compared with the monotherapy group, the dual therapy group had a significant increase in the number of patients who withdrew because of adverse drug effects (four studies; n = 7,703; RR = 1.34; 95% CI, 1.19 to 1.51).

A 2008 randomized, non-placebo-controlled prospective study of 50 patients with moderate (New York Heart Association [NYHA] class II or III) heart failure compared patients receiving standard therapy with those on a similar regimen plus 300 mg of irbesartan (Avapro).<sup>2</sup> Patients in both groups received an ACE inhibitor, and the remainder of the heart failure regimen was similar between the two groups (84% to 88% on a diuretic; 64% on a beta blocker). The average age in each group was 66 and 69 years, respectively.

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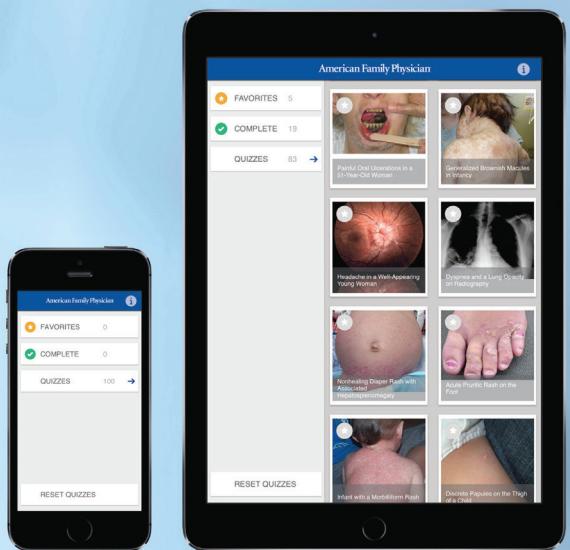
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## HELP DESK ANSWERS

Several disease-oriented outcomes were studied, as well as a composite outcome of mortality and/or cardiovascular hospitalization. At 12 months, a significant improvement was noted in the six-minute walk test distance (392 vs. 319 meters;  $P < .01$ ) and NYHA class (2.0 vs. 2.6;  $P < .01$ ). At 12 months, there was a significant improvement in metabolic equivalents achieved (4.6 vs. 3.1;  $P < .01$ ) and quality of life as measured by the Minnesota Living with Heart Failure Questionnaire (17 vs. 20, with lower scores indicating improved quality;  $P < .01$ ). The study did not find a significant difference between groups in the composite outcome of mortality and/or cardiovascular hospitalization (20% vs. 40%;  $P = .1$ ). Despite the difference in disease-oriented outcomes, the number of patients included in this study was not adequate to measure a difference in patient-oriented outcomes such as mortality and heart failure-related hospitalization.

The American College of Cardiology/American Heart Association released guidelines in 2013 on the diagnosis and management of heart failure.<sup>3</sup> They recommended an ACE inhibitor for all patients with heart failure and reduced ejection fraction (SOR: C, based on a guideline), or an ARB for patients who cannot tolerate ACE inhibitor therapy. They recommended adding an ARB to the current regimen for patients already receiving an ACE inhibitor who remain symptomatic or for those already receiving a beta blocker who are unable to take an aldosterone antagonist.

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3. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: executive summary. *Circulation*. 2013;128(16):1810-1852. ■