

ACE inhibitors vs. angiotensin II receptor blockers in acute myocardial infarction and heart failure

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Recent studies have led physicians to wonder whether angiotensin II receptor blockers (ARBs) now may be considered equivalent to ACE inhibitors as first-line treatment for post-infarct and heart failure patients. The short answer is probably not yet, except in a limited number of cases.

Until recently, ACE inhibitors were the undisputed drug of choice. The 1999 American College of Cardiology (ACC) guidelines for management of patients with acute myocardial infarction¹ do not mention ARBs. The 2001 ACC guidelines for evaluation and management of heart failure (HF)² state:

Angiotensin receptor blockers should not be considered equivalent or superior to ACE [angiotensin converting enzyme] inhibitors in the treatment of HF, and thus, they should not be used for

the treatment of HF in patients who have no prior use of an ACE inhibitor and should not be substituted for ACE inhibitors in patients who are tolerating ACE inhibitors without difficulty.

Since those guidelines were published, two large trials investigated the ARB candesartan. In one trial (CHARM-Alternative),³ candesartan was tested vs. placebo in a group of patients with reduced systolic function and heart failure who previously were found intolerant to ACE inhibitors. Candesartan reduced mortality and heart failure hospitalizations by 23%, similar to what has been achieved by ACE inhibitors tested in the past. A second study (CHARM-Added),⁴ tested the usefulness of combining an ACE inhibitor with candesartan in patients with heart failure. Such combined therapy further reduced mortality and heart failure hospitalizations by 15%, but its side effect profile was worse.

Another recent study, VALIANT,⁵ compared treatment with (a) the ARB valsartan alone, (b) the ACE inhibitor captopril alone, and (c) a combination of the two in patients with myocardial infarctions (MI) complicated by heart failure, left ventricular dysfunction, or both. It found no significant dif-

ferences among the three treatments in cardiovascular mortality or in subsequent major cardiovascular events. As with CHARM-Added, the side effect profile of combined therapy was worse than when either drug was used alone. The study design allowed the authors to compare valsartan and captopril head-to-head, and to conclude that valsartan is at least as effective as captopril in reducing the risk of such events.

The favorable results of VALIANT and CHARM have not been seen in all trials of ARBs. OPTIMAAL,⁶ a previous trial, compared the effects of ARB losartan with captopril in post-infarct patients, and found that patients receiving captopril had significantly lower rates of cardiovascular mortality and morbidity. Similarly, results of the ELITE II trial⁷ in heart failure patients failed to prove losartan superior to captopril. It may be that too small a dose of losartan was tested in both of these trials. As measured by decreases in blood pressure, the dose of valsartan in VALIANT was substantially higher, relatively speaking, than the doses of losartan in OPTIMAAL and ELITE II.

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The differences in outcome using losartan, as compared to the new trials with valsartan and candesartan, also raise the question of whether the results achieved by valsartan and candesartan can be assumed to apply to other ARBs in a “class effect.” The differences in pharmacologic profile among the various ARBs, the lack of direct trials post-infarction and in heart failure for many of the ARBs, and the differences in trial outcomes among those tested should lead us to be cautious in making such an assumption.

So, on the basis of current evidence, what can be recommended for post-infarct or heart failure patients who could benefit from one of these medications?

For post-infarct patients, we endorse the conclusion of the editorial accompanying the VALIANT results:⁸

Given that ACE inhibitors have been shown to reduce the risks of death and nonfatal cardiovascular events after acute myocardial infarction in 100,000 patients, whereas the clinical experience with angiotensin-receptor blockers has been more limited, and given that, in the United States, the cost of using valsartan at the doses used in [VALIANT] is approximately four to six times as high as the cost of using generic captopril at the doses used in this study, ACE inhibitors remain the logical first-line therapy for high-risk patients after acute myocardial infarction. However, for those patients who cannot tolerate ACE inhibitors, ...there now is a safe and equally effective alternative strategy....

The alternative strategy mentioned is valsartan, and not necessarily other ARBs, at an appropriately high dose.

With regard to heart failure patients, the evidence supporting the use of ARBs is weaker than in the post-MI case. ACE inhibitors remain the drug of choice in heart failure, with ARBs the clear alternative for those unable to take ACE inhibitors, based on the favorable effects of ARBs vs placebo in multiple trials.

A final, crucial point: An alarming number of post-infarct and heart failure patients with left ventricular dysfunction receive neither ACE inhibitors nor ARBs. In 2000-2001—when ACE inhibitors clearly were the treatment of choice—26% of eligible Medicare patients did not receive an ACE inhibitor post-MI, 30% of patients admitted for heart failure did not have a documented evaluation of their ejection fraction, and a full 32% of eligible patients hospitalized for heart failure with documented left ventricular dysfunction failed to receive an ACE inhibitor.⁹ As the recent trials show, patients are much better off with something—whether ACE inhibitor or ARB—than with nothing, and too often they are getting nothing.

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