Angiotensin II type 1 receptor blockers (ARBs) are generally as effective as angiotensin-converting enzyme (ACE) inhibitors in patients with hypertension. However, inhibition of angiotensin is not achieved completely through the blocking effects of ACE inhibitors, and the possibility of a non-ACE pathway for generation of angiotensin II has important implications for treating cardiovascular disease. The selective quality of ARBs for the angiotensin II type 1 (AT₁) receptor may confer an advantage. In a recently reported trial, the ARB valsartan substantially improved patients’ New York Heart Association class, clinical signs and symptoms, and quality of life and provided morbidity and mortality benefits in selected patients. Valsartan was recently approved to treat heart failure in patients who cannot be maintained on an ACE inhibitor. As a class, ARBs are well tolerated and have a good safety profile.


ACE = angiotensin-converting enzyme; ARB = angiotensin II type 1 receptor blocker; AT₁ = angiotensin II type 1; AT₂ = angiotensin II type 2; CHARM = Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity; ELITE = Evaluation of Losartan in the Elderly; ELITE II = Losartan Heart Failure Survival Study; NYHA = New York Heart Association; RAS = renin-angiotensin system; RESOLVD = Randomized Evaluation of Strategies for Left Ventricular Dysfunction; Val-HeFT = Valsartan Heart Failure Trial

The deleterious effects of angiotensin II on the heart and kidneys, known since the 1970s, have led to the therapeutic strategy of blocking the renin-angiotensin system (RAS).¹ ²  Evidence indicates that angiotensin is a local mediator that directly affects endothelial cells and smooth muscle cells and plays a major role in events that lead to disease.¹ Angiotensin-converting enzyme (ACE) inhibitors, the first effective blockers of the RAS, prevent formation of angiotensin II from angiotensin I. ACE inhibitors are used to treat hypertension, left ventricular dysfunction, heart failure, and diabetic renal disease; they also reduce the risk of coronary events in patients with preserved left ventricular function and such risk factors as diabetes, peripheral vascular disease, and coronary artery disease.³ However, not all patients can tolerate ACE inhibitors’ adverse effects of cough and angioedema.

Angiotensin II type 1 receptor blockers (ARBs), specific antagonists of the angiotensin II type 1 (AT₁) receptor subtype, are the newest therapeutic agents to counter effects of the RAS.³ ⁴ In patients with hypertension, ARBs are generally as effective as ACE inhibitors, without the ACE inhibitors’ limiting adverse effects. In patients with heart failure, ARBs decrease left ventricular filling pressures and pulmonary arterial pressures and improve cardiac output. In the Valsartan Heart Failure Trial (Val-HeFT), the ARB valsartan was found to provide morbidity and mortality benefits in selected patients who were not taking an ACE inhibitor, making this agent a viable therapeutic option for patients who cannot be maintained on ACE inhibitors.⁵

RENIN-ANGIOTENSIN SYSTEM
Angiotensin II is synthesized in a pathway that begins with the enzyme renin, secreted by the kidney in response to a decrease in blood pressure level. Renin cleaves a plasma substrate to release the inactive angiotensin I, which the ACE converts to the active hormone angiotensin II. Angiotensin II, the main biologically active peptide in the RAS cascade, is a potent vasoconstrictor and growth stimulator found in most tissue and in vascular endothelial cells.⁶ ⁷

Although the term renin-angiotensin system implies a single physiological entity, recent research has found this concept to be oversimplified. The RAS initially was thought of solely as a circulating endocrine system that quickly restored cardiovascular homeostasis if the blood pressure level suddenly decreased. However, we now know that less than 10% of the body’s ACE is found in the circulation, and the current view is that the RAS is primarily tissue based.⁸ ⁹ In contrast to the RAS in the circulatory...
system, tissue-based RAS has long-term effects that can modify cardiovascular function and structure.\textsuperscript{6} Angiotensin II affects multiple organs and structures, mediated through the AT\textsubscript{1} receptor. Vascular angiotensin induces vasoconstriction and stimulates vascular hypertrophy, effects that may promote development of subsequent atherosclerosis.\textsuperscript{6} Cardiac angiotensin stimulates myocyte hypertrophy and contributes to subendocardial ischemia;\textsuperscript{6} stimulation of fibroblasts produces cardiac fibrosis. Enhanced activity of plasminogen activator inhibitor 1 leads to impaired fibrinolysis. In the kidneys, angiotensin II triggers efferent arteriolar constriction, resulting in microalbuminuria. Thus, the tissue-based RAS and its principal mediator, angiotensin II, contribute to the development and progression of hypertension, arterial disease, cardiac hypertrophy, heart failure, and diabetic renal disease.\textsuperscript{1,4,6}

**BLOCKING THE RAS CASCADE**

The renin-angiotensin pathway can be interrupted pharmacologically in 2 ways: inhibition of ACE activity to prevent formation of angiotensin II (ACE inhibitors) or blockade of angiotensin II receptors (ARBs). The ARBs directly target angiotensin II by occupying its receptor sites and forestalling its effects. This is an especially important attribute because ACE is not the only enzyme that can convert angiotensin I to angiotensin II; alternative pathways are mediated by the enzymes trypsin, cathepsin, tonin, and heart chymase.\textsuperscript{7} Inhibition of angiotensin II is not achieved completely through the blocking effects of ACE inhibitors; the possibility of a non-ACE pathway for generation of angiotensin II, likely involving chymase, has important implications for treating cardiovascular disease.\textsuperscript{8} Of the 6 ARBs approved for clinical use in hypertension (candesartan cilexetil, eprosartan mesylate, irbesartan, losartan, telmisartan, and valsartan), valsartan has proven effective.

**CHARACTERISTICS OF ARBs**

Evidence indicates that ARBs, like ACE inhibitors, lower arterial pressure without causing reflex tachycardia.\textsuperscript{4} Several mechanisms may be involved, but inhibition of the vasoconstrictive effect of angiotensin II has the greatest clinical importance.\textsuperscript{9} The antihypertensive efficacy of ARBs compares with that of other agents. Their full blood pressure–lowering effect takes 4 to 6 weeks to develop.\textsuperscript{5,11}

Whereas ACE inhibitors increase bradykinin levels, the specific blockade of the AT\textsubscript{1} receptor provided by ARBs has been presumed to avoid this effect on bradykinin,\textsuperscript{12} although recent experimental work has challenged this concept.\textsuperscript{13} Elevated bradykinin levels are believed to be responsible for the cough that is a frequent adverse effect of ACE inhibition, but bradykinin also has vasodilatory benefits and may be involved in the reversal of endothelial dysfunction.\textsuperscript{7} As a class, ARBs are well tolerated and have a good safety profile.\textsuperscript{11} Like ACE inhibitors, ARBs can cause hyperkalemia and persistent elevation in creatinine.

**CLINICAL TRIALS OF ARBS IN HEART FAILURE**

Several trials have been conducted to assess the role of ARBs in treating heart failure (Table 1).

**Evaluation of Losartan in the Elderly Trial**

The Evaluation of Losartan in the Elderly (ELITE) trial compared the effects of losartan and captopril in 722 men and women aged 65 years and older with symptomatic New York Heart Association (NYHA) class II to IV heart failure and ejection fractions of 40% or less.\textsuperscript{14} All patients were ACE inhibitor–naive. The primary end point was increase in serum creatinine by 0.3 mg/dL or more from baseline. The 48-week study showed no difference between losartan and captopril for improving NYHA class (P<.001) or frequency of persisting increases in serum creatinine (10.5% in both groups). However, risk of a tertiary end point—death and/or hospital admission for heart failure—was reduced 32% primarily because of reduced all-cause mortality in the losartan group, 4.8% vs 8.7% in the captopril group (P=.04). Losartan was generally better tolerated, and significantly fewer patients in the ARB group (12.2%) discontinued treatment with losartan because of adverse effects than in the ACE inhibitor group (20.8%) using captopril (P<.002).\textsuperscript{14}

**Losartan Heart Failure Survival Study**

Although ELITE was not designed as a mortality trial, an apparent 46% reduction in all-cause mortality (tertiary end point) primarily due to a reduction in sudden death prompted initiation of a second, considerably larger mortality end point trial. The Losartan Heart Failure Survival Study (ELITE II) randomly assigned patients to treatment...
Table 1. Randomized, Double-Blind, Placebo-Controlled Clinical Trials of Angiotensin II Type 1 Receptor Blockers in Patients With Heart Failure (NYHA Classes II-IV)*

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drugs</th>
<th>Study population of men and women</th>
<th>Duration</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELITE</td>
<td>Losartan, 50 mg/d vs captopril, 50 mg 3 times per day</td>
<td>722 patients ≥65 y; LVEF, &lt;40%</td>
<td>48 wk</td>
<td>Both drugs reduced LV volume; no difference in tolerability</td>
</tr>
<tr>
<td>ELITE II</td>
<td>Losartan, 50 mg/d vs captopril, 50 mg 3 times per day</td>
<td>3152 patients ≥60 y; LVEF, &lt;40%; symptomatic heart failure</td>
<td>555 d (median)</td>
<td>No difference in all-cause mortality; losartan better tolerated</td>
</tr>
<tr>
<td>RESOLVD</td>
<td>Candesartan cilexetil, enalapril, or both</td>
<td>768 patients; LVEF, &lt;40%; 6-min walk distance, &lt;500 m</td>
<td>43 wk</td>
<td>Combination therapy increased LVEF; more complete neurohormonal blockade</td>
</tr>
<tr>
<td>Val-HeFT</td>
<td>Valsartan, 160 mg 2 times per day or placebo added to standard therapy</td>
<td>5010 patients; LVEF, &lt;40%</td>
<td>27 mo</td>
<td>Significant reductions in combined morbidity and mortality; improved NYHA class, signs and symptoms, and quality of life</td>
</tr>
</tbody>
</table>

*ELITE = Evaluation of Losartan in the Elderly; ELITE II = Losartan Heart Failure Survival Study; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; RESOLVD = Randomized Evaluation of Strategies for Left Ventricular Dysfunction; Val-HeFT = Valsartan Heart Failure Trial.

with losartan or captopril (same doses as were used in the ELITE trial). The primary outcome measure was all-cause mortality, and secondary end points were sudden death or resuscitated arrest.\(^{15}\)

No significant differences were observed between losartan and captopril in all-cause mortality, sudden death, or resuscitated arrests. However, significantly fewer patients discontinued treatment with losartan than with captopril because of adverse effects (9.7\% vs 14.7\%; \(P<.001\)).\(^{15}\) The researchers suggested that ACE inhibitors should be the initial treatment of heart failure and that ARBs may be useful when ACE inhibitors are not tolerated. Because this trial was not powered for noninferiority but for superiority, the results cannot be used to assess whether losartan is effective for treating heart failure.

Randomized Evaluation of Strategies for Left Ventricular Dysfunction

The Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) pilot study was the first to compare an ACE inhibitor, an ARB, and their combination in patients with heart failure.\(^{16}\) The rationale was that an ARB would block the deleterious effects of angiotensin II at the receptor level while the ACE inhibitor would potentiate the vasodilatory effects of bradykinin. Accordingly, 768 patients with NYHA class II to IV heart failure and ejection fractions less than 40% were randomly assigned to enalapril, candesartan, or the combination for 43 weeks.\(^{16}\) The primary end points were exercise capacity, safety, and tolerability.

RESOLVD terminated early because of the presumed negative effects of combined enalapril and candesartan compared with either therapy alone. However, RESOLVD was not designed as a mortality trial. Also, in the combined treatment group, left ventricular ejection fractions increased more and serum aldosterone and brain natriuretic peptide decreased more than with either drug alone.\(^{16}\) The researchers concluded that the combination of an ACE inhibitor and an ARB may provide more benefit in preventing left ventricular dilation than either class alone and that combination therapy achieved a more complete blockade of the RAS than did either agent alone.\(^{16}\) RESOLVD served as the pilot for the larger ongoing Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) study (discussed subsequently).

Valsartan Heart Failure Trial

The Valsartan Heart Failure Trial (Val-HeFT) was the first ARB trial to show morbidity and mortality benefits in patients with heart failure who were not taking an ACE inhibitor. Valsartan or placebo was added to standard treatment—a fixed-dose regimen of at least 2 weeks’ duration that included ACE inhibitors, diuretics, digoxin, and β-blockers—in 5010 men and women with NYHA class II to IV heart failure, ejection fractions less than 40%, and left ventricular dilation.\(^{3}\) The co-primary end points were mortality and the combined end point of mortality and morbidity, defined as hospitalization for heart failure, cardiac arrest with resuscitation, or administration of an inotropic agent or vasodilator for 4 hours or more.

After 27 months, valsartan added to standard therapy had no significant impact on mortality compared with placebo. However, the combined end point of morbidity and mortality was significantly reduced (\(P=.009\)) in patients who received valsartan. The difference between the groups emerged early in treatment and increased throughout the trial, amounting to a 13.2\% risk reduction in combined morbidity and mortality largely due to a 24\% reduction in (adjudicated) first hospitalizations for patients treated with valsartan (\(P<.001\)). Subsequent (nonadjudicated) hospitalizations were reduced by 27.5\% in the valsartan group. Compared with standard treatment alone, the addition of
valsartan significantly improved patients’ NYHA functional class, clinical signs and symptoms, and quality of life. Patients who were not taking an ACE inhibitor and received valsartan (7% of patients) during the trial experienced a 44.5% risk reduction for morbidity and a 33% risk reduction in mortality compared with placebo. Significant hemodynamic and neurohormonal improvements were seen in the valsartan group compared with the non–ACE inhibitor subgroup. At the last study observation, the valsartan group had a significant increase in left ventricular ejection fraction (P=.01) and a significant decrease in left ventricular internal dimension in diastole/body surface area (P<.001). The valsartan-treated group had a nonsignificant attenuated increase in norepinephrine (P=.21) and a significant decrease in plasma brain natriuretic peptide levels (P<.001). Secondary clinical outcomes of significantly decreased blood pressure levels without reflex tachycardia (P=.004) and increased walking time (P=.02) were observed in the valsartan group compared with those treated without an ACE inhibitor. However, the Val-HeFT investigators noted one important caveat: for the subgroup of patients who entered the study being treated with both an ACE inhibitor and a β-blocker (35%), the addition of valsartan adversely affected mortality and morbidity. The Val-HeFT researchers stressed that this finding, based on a small number of patients, needs clarification.

The Val-HeFT findings confirmed an earlier study of valsartan in patients with heart failure in which, compared with placebo, valsartan significantly reduced pulmonary capillary wedge pressure (40-mg and 160-mg doses), decreased systemic vascular resistance (all doses), and increased cardiac output (80-mg and 160-mg doses). Lisinopril was included in the study to validate rather than research its use acceptable when patients cannot continue ACE inhibition. As well as the effects of multiple neurohormonal blockade. The VALIANT study will observe 14,500 post–myocardial infarction patients with heart failure and left ventricular ejection fraction (LVEF) less than 40% who are not being treated with an ACE inhibitor. It is expected that the number of patients in CHARM on concomitant β-blocker therapy will be higher than that in Val-HeFT, which may help answer questions relating to triple neurohormonal blockade. Also, the results in the ACE-intolerant group will either confirm or contradict the observations made of ACE-intolerant patients in RESOLVD. The Valsartan in Acute Myocardial Infarction (VALIANT) study will observe 14,500 post–myocardial infarction patients with heart failure and left ventricular dysfunction treated with the ARB valsartan only, with the ACE inhibitor captopril only, and with a combination of valsartan and captopril. The end point is all-cause mortality.

CONCLUSIONS
ACE inhibitors remain first-line therapy for patients with heart failure. However, ARBs are a logical choice for patients who cannot be maintained on ACE inhibition. The reductions in morbidity and mortality observed in the non-ACE subgroup in Val-HeFT should give clinicians confidence in choosing an ARB when ACE inhibition is not feasible. Angiotensin II type 1 receptor blockers are well tolerated and have a low adverse effect profile that makes their use acceptable when patients cannot continue ACE inhibition therapy. The results of ongoing trials are awaited to elucidate further the role of ARBs in specific patient population groups and in those receiving concurrent therapy with other medications, eg, β-blockers without ACE inhibition, as well as the effects of multiple neurohormonal blockade.

REFERENCES
3. Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting–enzyme inhibitor, ramipril, on
Questions About ARBs

1. Which one of the following is the best explanation of how ARBs exert their physiological and therapeutic effects?
   a. ARBs combine with ACE to decrease production of angiotensin II
   b. ARBs increase levels of active bradykinin by indirectly up-regulating angiotensin II
   c. ARBs block the angiotensin II receptor to decrease the effects of angiotensin II
   d. ARBs ultimately decrease renin production
   e. ARBs selectively block the AT2 receptor

2. Which one of the following is the only clinical use for ARBs?
   a. Antihypertensive therapy
   b. Antioxidants
   c. Renal failure
   d. Antihypertensive and heart failure therapy
   e. ACE inhibitor–intolerant patients

3. Which one of the following is correct about ARB use for heart failure?
   a. ARBs are considered equivalent to ACE inhibitors
   b. ARBs are safe and a acceptable alternative to ACE inhibitors in ACE inhibitor–intolerant patients
   c. Adding an ARB to a β-blocker and ACE inhibitor was proved to be a contraindication
   d. ARBs were proved superior to ACE inhibitors
   e. ARBs were proved superior to β-blockers

4. Which one of the following is a possible adverse effect of ARBs?
   a. Reflex tachycardia
   b. Cough
   c. Hyperkalemia
   d. Rebound hypertension
   e. Bradycardia

5. In which one of the following have the doses of ARBs been adequately studied?
   a. Hypertension
   b. Heart failure
   c. Renal failure
   d. Liver failure
   e. Pulmonary hypertension

Correct answers:
1. c, 2. d, 3. b, 4. c, 5. a