Debate: Angiotensin-Converting Enzyme Inhibitors Versus Angiotensin II Receptor Blockers—A Gap in Evidence-Based Medicine

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In this article, 2 leading physicians debate the strength of outcome data on the efficacy of angiotensin-converting enzyme (ACE) inhibitors versus angiotensin II receptor blockers (ARBs) for reducing the incidence of cardiovascular, cerebrovascular, and renovascular events. Dr. Stephen G. Ball notes that the efficacy of ACE inhibitors for reducing the risk for myocardial infarction independent of their effects on blood pressure is controversial. In the Heart Outcomes Prevention Evaluation (HOPE) study, ramipril treatment in high-risk patients was associated with a 20% reduction in the risk for myocardial infarction; mean reduction in blood pressure was 3 mm Hg for systolic blood pressure and 1 mm Hg for diastolic blood pressure. The HOPE investigators propose that the 20% reduction was much greater than would be expected based on the observed blood pressure reduction. However, a meta-regression analysis of blood pressure reduction in >20 antihypertensive therapy outcome trials found that the reduction in myocardial infarction risk with ramipril observed in HOPE was consistent with the modest blood pressure reduction seen with that agent. Nevertheless, there are convincing data for prevention of myocardial infarction with ACE inhibitors in patients with heart failure, including those with heart failure after myocardial infarction, as well as supportive evidence from studies in patients with diabetes mellitus and concomitant hypertension. On the other hand, Dr. William B. White takes the position that ARBs are well-tolerated antihypertensive agents that specifically antagonize the angiotensin II type 1 (AT₁) receptor and provide a more complete block of the pathologic effects of angiotensin II—which are mediated via the AT₁ receptor—than ACE inhibitors. The Evaluation of Losartan in the Elderly (ELITE) II study and the Valsartan Heart Failure Trial (ValHeFT) suggest that ARBs reduce the risk for mortality in patients with congestive heart failure. The Losartan Intervention for Endpoint (LIFE) Reduction in Hypertension trial also demonstrated beneficial effects of ARBs in the prevention of stroke events. The Irbesartan in Patients with Diabetes and Microalbuminuria (IRMA) study, the Irbesartan Diabetic Nephropathy Trial (IDNT), and the Reduction of Endpoint in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study demonstrated significant reductions in the rate of progression of renal disease in patients receiving ARBs, independent of effects on blood pressure. These data support the use of ARBs, in addition to the standard of care, in hypertensive patients with heart failure who are intolerant of ACE inhibitors, and also provide compelling evidence for their use in patients with hypertension and type 2 diabetes. ©2003 by Excerpta Medica, Inc.

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TREATMENT WITH ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

(Dr. Ball) The goal of treatment with antihypertensive agents is not the lowering of blood pressure itself, but the prevention of cardiovascular events. The efficacy of ACE inhibitors for reducing morbidity and mortality in patients with heart failure has been shown in numerous studies. A meta-analysis of data from 7,105 patients with symptomatic congestive heart failure in 32 randomized trials that were ≥8 weeks in duration demonstrated a significant reduction in all-cause mortality (odds ratio, 1.07; 95% confidence interval, 0.67 to 0.88; p <0.001) and mortality plus hospitalization caused by congestive heart failure (odds ratio, 0.65; 95% confidence interval, 0.57 to 0.74; p <0.001) with ACE inhibitor therapy (along with usual therapy) compared with placebo.² The decrease in total mortality was largely attributed to a significant reduction in death caused by progressive heart failure (odds ratio, 0.69; 95% confidence interval, 0.58 to 0.83).² A separate meta-analysis of 5
long-term randomized trials of ACE inhibitor treatment (in addition to standard care) involving 12,763 patients with left ventricular dysfunction or heart failure with or without recent myocardial infarction (MI) showed significant reductions in all-cause mortality (odds ratio, 0.80; 95% confidence interval, 0.74 to 0.87), hospitalization because of heart failure (odds ratio, 0.67; 95% confidence interval, 0.61 to 0.74), and reinfarction compared with placebo (odds ratio, 0.79; 95% confidence interval, 0.70 to 0.89).\(^3\) The effects of ACE inhibitor therapy (in addition to routine care) on patients during the early phase after MI (started 0 to 36 hours after onset and continued for 4 to 6 weeks) were evaluated in a meta-analysis involving 98,496 patients in 4 randomized trials.\(^4\) Therapy with an ACE inhibitor was associated with a 7% reduction in 30-day mortality (95% confidence interval, 2% to 11%; \(p < 0.004\)) and a decrease in nonfatal heart failure (14.6% with ACE inhibitors compared with 15.2% for placebo, \(p < 0.01\)).

ACE inhibitors decrease circulating levels of angiotensin II, which has been implicated in atherosclerosis and other processes that contribute to coronary artery disease.\(^5\) On that basis, there has been speculation that ACE inhibitors may reduce the risk for coronary events independently of their ability to lower blood pressure.

Cardioprotective benefits of ACE inhibitors have been claimed for hypertensive patients with type 2 diabetes mellitus. These agents were found to lower the risk for cardiovascular events compared with calcium antagonist therapy in the Fosinopril versus Amldipine Cardiovascular Events Randomized Trial (FACET) and the Appropriate Blood Pressure Control in Diabetes (ABCD) Trial, which were randomized, active-controlled studies that enrolled patients with type 2 diabetes and concomitant hypertension. In FACET (n = 380), patients receiving fosinopril demonstrated a significantly lower risk for the primary outcome, which was a combined end point consisting of acute MI, stroke, and hospitalization because of angina, compared with patients receiving amldipine (hazard ratio, 0.49; 95% confidence interval, 0.26 to 0.95).\(^6\) This occurred despite significantly greater reduction in systolic blood pressure in the amldipine group compared with the fosinopril group (\(-19\) mm Hg for amldipine vs \(-13\) mm Hg for fosinopril; \(p < 0.05\)) and identical mean changes in diastolic blood pressure in both groups (\(-8\) mm Hg). In ABCD (n = 470), the enalapril group had a significantly lower risk for MI (fatal and nonfatal) compared with patients receiving nisoldipine (adjusted risk ratio, 7.0; 95% confidence interval, 2.3 to 21.4), although the effects of these 2 agents on blood pressure were not significantly different.\(^7\) However, these trials were small with few end points, and their findings must be regarded with caution, especially in light of the findings from the numerous large-scale trials, which randomized substantial numbers of patients with diabetes.\(^8\)\(^9\) Furthermore in the UK Prospective Diabetes Study (UKPDS) of “tight control” of blood pressure, no advantage of captopril was found over atenolol.\(^10\)

In trials recruiting patients with increased blood pressure, the efficacy data of ACE inhibitors for reducing the risk for cardiovascular events, such as MI, separately from their effects on blood pressure have been conflicting. The Swedish Trial in Old Patients (STOP) with Hypertension-2 included comparisons in cardiovascular outcomes for 6,614 patients aged 70 to 84 with hypertension randomized to \(\beta\)-blockers or diuretics, calcium antagonists, and ACE inhibitors.\(^11\) Mean systolic and diastolic blood pressure differed by \(\leq 2\) mm Hg among the 3 treatment groups throughout the study (the groups’ mean blood pressures were identical at baseline). The risk for MI (fatal and nonfatal) with ACE inhibitor therapy or \(\beta\)-blocker and diuretic treatment was not significantly different (relative risk, 0.90; 95% confidence interval, 0.72 to 1.13; \(p = 0.38\)). In contrast, risk for MI with ACE inhibitor therapy was significantly lower than with calcium antagonist treatment (relative risk, 0.77; 95% CI, 0.61 to 0.96; \(p = 0.018\)). In the Captopril Prevention Project (CAPPP), 10,985 patients with hypertension were randomized to captopril or a conventional therapy of diuretics, \(\beta\)-blockers, or both.\(^12\) At baseline, mean systolic blood pressure was 2.2 mm Hg higher and mean diastolic blood pressure was 1.7 mm Hg higher in the captopril group compared with the \(\beta\)-blocker–diuretic group. The risk for fatal and nonfatal MI was not significantly different for the captopril and \(\beta\)-blocker–diuretic groups (relative risk, 0.96; 95% confidence interval, 0.73 to 1.20; \(p = 0.68\)). The results of the CAPPP study have been criticized because of the baseline differences in blood pressure among the treatment groups.

The Heart Outcomes Prevention Evaluation (HOPE) trial was designed to assess the effects of ACE inhibitors on cardiovascular outcomes in the absence of effects on blood pressure.\(^13\) The HOPE trial enrolled 9,297 patients at elevated risk for cardiovascular events (aged \(\geq 55\) years and with a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes, plus \(\geq 1\) of the following: hypertension, elevated total cholesterol, decreased high-density lipoprotein cholesterol, cigarette smoking, or microalbuminuria). Heart failure, low ejection fraction \((<0.40)\), and an MI or stroke during the 4 weeks before the study were reasons for exclusion (as were uncontrolled hypertension, overt nephropathy, and use of vitamin E or an ACE inhibitor). Eligible patients were randomized to ramipril 10 mg once daily or matching placebo. At the conclusion of the study, the difference in blood pressure between the ramipril and placebo groups was \(3\) mm Hg for systolic and \(1\) mm Hg for diastolic. The risk of the primary outcome, a combined end point consisting of MI, stroke, or death from cardiovascular causes, was significantly lower for the ramipril group compared with the placebo group (\(p < 0.001\); Table 1). The risk of death from any cause was also significantly lower for the ramipril group (\(p = 0.005\)), but the risk of death from noncardiovascular causes was not significantly different be-
between the 2 groups (p = 0.74). The risk of MI was 9.9% among patients receiving ramipril and 12.3% among patients receiving placebo, with a 20% lower relative risk with ramipril (p < 0.001).

The HOPE investigators have proposed that the 20% reduction in risk for MI seen with ramipril in the HOPE study is much greater than would be expected based on the blood pressure reductions achieved with that agent. According to estimates based on a meta-analysis reported by Sleight et al., the expected reduction in MI risk for a population exhibiting a mean decrease in systolic blood pressure of 3 mm Hg would be 5%. On that basis, the effect of ramipril treatment on MI risk would appear to be because of factors other than lowering of blood pressure.

A meta-regression analysis of outcome trial data by Staessen et al.* suggests that the benefits of ramipril treatment seen in the HOPE study might be explained entirely by the observed decrease in systolic blood pressure. The odds ratio for MI was plotted according to the difference in systolic blood pressure between the treatments compared in each of >20 separate trials, and curves representing the mean and 95% confidence interval were calculated using regression analysis. As shown in Figure 1, the results for HOPE were within the 95% confidence interval for this meta-regression analysis. The predicted mean odds ratio for MI in HOPE based on the placebo-subtracted change in systolic blood pressure in this analysis was 0.85, with 95% confidence interval, 0.77 to 0.93 showing a clear overlap with the observed 0.79 (95% confidence interval, 0.69 to 0.90) risk reduction.

Data on the efficacy of an ACE inhibitor for preventing MI, although not beyond its ability to reduce blood pressure when combined with a diuretic, were also obtained in the recent Perindopril Protection Against Recurrent Stroke Study (PROGRESS). This trial enrolled patients with a history of stroke or transient ischemic attack and without heart failure or other indication for ACE inhibitor treatment. A total of 6,105 patients were randomized to perindopril 4 mg/day plus indapamide 2.5 mg/day (indapamide 2.0 mg for patients in Japan) or placebo. Active treatment was associated with mean blood pressure reductions of 9 mm Hg systolic and 4 mm Hg diastolic compared with placebo. The risk for major coronary events was reduced by 26% (95% confidence interval, 6% to 42%) for patients receiving active treatment versus placebo, which is consistent with the blood pressure reduction seen in this trial.

At present, there are convincing data on end-organ protection with ACE inhibitors for patients with heart failure, including those with heart failure after MI, and for patients with diabetes and concomitant hypertension, including those at risk for progressive nephropathy. Blocking the renin–angiotensin system with these agents appears to add more than simply the effect of blood pressure reduction. There are 2 ongoing large outcome studies that will provide important additional data on the use of ACE inhibitors to prevent acute MI in patients with coronary artery disease but with normal heart function: the Prevention of Events With Angiotensin Converting Enzyme Inhibition (PEACE) study and the European Trial on Reduction of Cardiac Events with Perindopril (EUROPA).16,17

### ANGIOTENSIN II RECEPTOR BLOCKERS: NEW ROLES IN CARDIOVASCULAR THERAPEUTICS

(Dr. White) ACE inhibitors are effective agents for lowering blood pressure and reducing the risk for cardiovascular events and progressive renal disease, but these agents are not well tolerated by some patients because of treatment-associated dry cough and angioedema. In addition, these drugs do not provide a complete block of angiotensin II synthesis because of alternate, non-ACE pathways. Chymase, which is not blocked by ACE inhibitors, participates in local synthesis of angiotensin II in cardiac tissues, especially in the left ventricle. Locally synthesized angiotensin II, acting on AT1 receptors, has been associated with hypertrophy of cardiac muscle.5,18 In contrast, ARBs specifically antagonize the AT1 receptor and thus may provide a more complete block of the pathologic effect of angiotensin II, which is mediated via the AT1 receptor.5

The renin–angiotensin system exhibits circadian variation, with renin and angiotensin II levels low in the early evening but increasing markedly by the early morning hours. The early morning increase in renin–angiotensin activation is believed to contribute in part to the early morning increase in blood pressure and the potential for greater risk for cardiovascular events during this period. Thus, blood pressure control dur-

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**Table 1: Incidence of Primary End Points in the Heart Outcomes Prevention Evaluation Study**

<table>
<thead>
<tr>
<th>End Point</th>
<th>Ramipril (n = 4,645)*</th>
<th>Placebo (n = 4,652)</th>
<th>Relative Risk (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined endpoint of myocardial infarction and death due to CV causes</td>
<td>651 (14.0)</td>
<td>826 (17.8)</td>
<td>0.78 (0.70–0.86)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death from CV causes</td>
<td>282 (6.1)</td>
<td>377 (8.1)</td>
<td>0.74 (0.64–0.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>459 (9.9)</td>
<td>570 (12.3)</td>
<td>0.80 (0.70–0.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>156 (3.4)</td>
<td>226 (4.9)</td>
<td>0.68 (0.56–0.84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death from noncardiovascular causes</td>
<td>200 (4.3)</td>
<td>192 (4.1)</td>
<td>1.03 (0.85–1.26)</td>
<td>0.74</td>
</tr>
<tr>
<td>Death, all-cause</td>
<td>482 (10.4)</td>
<td>569 (12.2)</td>
<td>0.84 (0.75–0.95)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

*Percentages are in parentheses;
CI = confidence interval; CV = cardiovascular.
Adapted from N Engl J Med.13
ing the early morning hours before dosing may be important for reducing cardiovascular risk. The calcium antagonist amlodipine, which has an inherent half-life of approximately 30 hours, has been shown to be an effective once-daily antihypertensive. Telmisartan, the ARB with the longest plasma half-life (approximately 24 hours), was recently studied in a clinical trial comparing it with amlodipine. The diastolic blood pressure at night and during the 4 hours before dosing (p < 0.05) was reduced to a greater extent by telmisartan compared with amlodipine. Systolic blood pressure reduction with telmisartan was consistent throughout the 24-hour dosing interval and compared favorably with that of amlodipine (Figure 2). To my knowledge, none of the ACE inhibitors have been shown to have greater antihypertensive

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**FIGURE 1.** Relation between odds ratio for myocardial infarction (fatal and nonfatal) and difference between experimental and reference treatment with respect to change in blood pressure from baseline for various randomized outcome trials. Curves were plotted using meta-regression analysis; broken lines indicate the 95% confidence intervals. Closed circles denote trials that compared new with old drugs. ACEIs = Angiotensin-converting Enzyme arm of the STOP2 trial; ALLHAT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ATMH = Australian Trial in Mild Hypertension; CAPP = Captopril Prevention Project; CCBs = calcium-channel blocker arm of the STOP2 trial; EWPHE = European Working Party on High Blood Pressure in the Elderly; HEP = Hypertension in Elderly Patients in Primary Care; HOPE = Heart Outcomes Prevention Evaluation; HOT M vs H = Hypertension Optimal Treatment trial (85 vs 90 mm Hg as target diastolic pressure); HOT L vs H = Hypertension Optimal Treatment trial (80 vs 90 mm Hg as target diastolic pressure); INSIGHT = International Nifedipine GITS Study-Intervention as a Goal for Hypertension Therapy; MIDAS = MIDAS Multicenter Isradipine-Diuretic Atherosclerosis Study; MRC1 = Medical Research Council Trial of Treatment of Mild Hypertension; MRC2 = Medical Research Council trial of Treatment of Hypertension in Older Adults; NICS = NonInvasive Carotid Study; NORDIL = Nordic Diltiazem Study; PART2 = Prevention of Atherosclerosis with Ramipril Trial; PROGRESS = Perindopril Protection Against Recurrent Stroke Study; RCT 70–80 = combined results of 4 smaller trials published from 1970 through 1980, including HSCS, OSLO, USPHS, and VACS; SBP = systolic blood pressure; SCAT = Simvastatin/Enalapril Coronary Atherosclerosis Trial; SHEP = Systolic Hypertension in the Elderly; STONE = Shanghai Trial of Nifedipine in the Elderly; STOP1 = Swedish Trial in Old Patients with Hypertension study; STOP2 = Swedish Trial in Old Patients with Hypertension-2 study; Syst-China = Systolic Hypertension in China trial; Syst-Eur = Systolic Hypertension in Europe trial; UKPDS C vs A = UKPDS Hypertension in Diabetes Study-Captopril versus Atenolol; UKPDS L vs H = UKPDS Hypertension in Diabetes Study-Low versus High On-Treatment Blood Pressure; VHAS = Verapamil in Hypertension and Atherosclerosis Study. (Reprinted with permission from Lancet.9)
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cia compared with amlodipine for lowering blood pressure during the hours before dosing.

**RECENT OUTCOME TRIALS WITH THE ANGIOTENSIN II RECEPTOR BLOCKERS**

The efficacy of ARBs for treating patients with heart failure has been studied in 2 large trials, the Evaluation of Losartan in the Elderly (ELITE) II study and the Valsartan Heart Failure Trial (ValHeFT). The ELITE II study, which was designed as a superiority study, compared the efficacy of losartan 50 mg/day with captopril 150 mg/day for improving survival in 3,152 patients with heart failure.24 The ValHeFT study assessed the efficacy of valsartan 320 mg/day added to standard therapy for reducing morbidity and mortality in 5,010 patients with heart failure.25

In the ELITE II study, the rates of all-cause mortality and sudden death or resuscitated arrests for the losartan group were not significantly different from that for the captopril group (hazards ratio for total mortality, 1.13, and 95% confidence interval, 0.95 to 1.35; hazards ratio for sudden death or resuscitated arrests, 1.25, and 95% confidence interval, 0.98 to 1.60). The rate of discontinuation because of drug-related adverse events and cough was significantly lower for the losartan group than the captopril group (p ≤0.001),24 consistent with the excellent tolerability profile associated with ARBs.

In ValHeFT, patients received valsartan or placebo in addition to standard therapy, which included ACE inhibitors (93% of the patients), diuretics (86%), digoxin (67%), and β-blockers (35%).25 Patients receiving valsartan demonstrated a 13.2% reduction in the combined end point of mortality and morbidity (defined as the incidence of cardiac arrest with resuscitation, hospitalization for heart failure, or receipt of intravenous inotropic or vasodilator therapy for ≥4 hours) compared with patients receiving placebo. Treatment with valsartan was associated with a significantly lower rate of hospitalization for heart failure and a significantly lower incidence of the combined end point of cardiac arrest with resuscitation plus hospitalization for heart failure plus use of intravenous inotropic or vasodilator therapy for ≥4 hours compared with placebo (p < 0.001 for hospitalization owing to heart failure; p = 0.009 for the combined end point.) Post hoc analyses of data based on concomitant therapy showed that valsartan treatment significantly reduced the incidence of the combined end point in patients also receiving an ACE inhibitor. For patients not receiving an ACE inhibitor, valsartan lowered the combined end point by 45%. For patients receiving both an ACE inhibitor and a β-blocker, the addition of valsartan was not associated with a benefit over placebo. Basing conclusions on these post hoc analyses warrants caution for the following reasons: (1) background therapy was not controlled, (2) patients were not stratified according to ACE inhibitor use, and (3) calculations were performed for the purpose of hypothesis generation.

The Losartan Intervention for Endpoint Reduction (LIFE) in Hypertension study compared the efficacy of losartan- and atenolol-based therapies for improving left ventricular hypertrophy and reducing cardiovascular morbidity and mortality in 9,193 patients with essential hypertension and left ventricular hypertrophy observed for ≥4 years.26 Mean reductions in blood pressure with the 2 therapies were similar (30.2/16.6 mm Hg in the losartan group; 29.1/16.8 mm Hg in the atenolol group). The risk for both the primary composite end point (death, MI, or stroke) and stroke was significantly lower for patients receiving losartan compared with those receiving atenolol (relative risk for primary end point, 0.87 and p = 0.021; relative risk for stroke, 0.75; p=0.001).

Perhaps the most important clinical outcome data with ARBs come from 3 recent studies that assessed the efficacy of these agents for protecting patients with
type 2 diabetes from development or progression of diabetic nephropathy: the Irbesartan in Patients with Diabetes and Microalbuminuria 2 (IRMA-2) study, the Irbesartan Diabetic Nephropathy Trial (IDNT), and the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL). Previous studies had established that ACE inhibitors slowed the progression of renal dysfunction in patients with type 1 diabetes, but conclusive data on patients with type 2 diabetes have been lacking. The IRMA-2, IDNT, and RENAAL results suggest that treatment with ARBs slowed the progression of renal disease in patients with type 2 diabetes, and this benefit was independent of blood pressure reduction.

The IRMA-2 study enrolled 590 patients with type 2 diabetes and microalbuminuria. These patients were randomized to irbesartan (150 mg/day and 300 mg/day) or placebo for 2 years. The primary end point was time to onset of diabetic nephropathy (consistent urinary albumin excretion rate >200 µg/min and ≥30% above baseline in overnight specimens). The primary end point was reached by 9.7% of patients receiving irbesartan 150 mg, 5.2% of patients receiving irbesartan 300 mg, and 14.9% of patients receiving placebo (p <0.001). Kaplan-Meier curves were significantly different for irbesartan 300 mg versus placebo (p <0.001). Mean diastolic blood pressure was the same for the 3 treatment groups (83 mm Hg), and the difference in systolic blood pressure between the irbesartan and placebo groups ranged from 1 to 3 mm Hg.

In IDNT, 1,715 patients with type 2 diabetes, macroproteinuria, and hypertension were randomized to irbesartan 300 mg, amiodipine 10 mg, or placebo; the mean duration of follow-up time was 2.6 years. The primary end point was a composite of the doubling of baseline serum creatinine level, development of end-stage renal disease, renal transplantation, and death (all cause). The irbesartan group demonstrated a 20% reduction in the primary end point compared with the placebo group (p = 0.02) and a 23% reduction in this end point compared with the amiodipine group (p = 0.006). The risk for doubling the serum creatinine level for the irbesartan group was 33% lower than for the placebo group (p = 0.003) and 37% lower than that for the amiodipine group (p <0.001). The risk of end-stage renal disease was 23% lower for the irbesartan group than for the placebo and amiodipine groups (p <0.07). Mean arterial pressure for the irbesartan and amiodipine groups was not significantly different.

In the RENAAL study, 1,513 patients with type 2 diabetes and nephropathy were randomized to losartan (50 mg/day and 100 mg/day) and placebo in addition to standard antihypertensive therapy; mean follow-up time was 3.4 years. The primary end point was a composite of the doubling of baseline serum creatinine level, development of end-stage renal disease, and death (all cause). Treatment with losartan was associated with a reduction in the risk for the primary end point of 16% (p = 0.02). The risk for doubling the serum creatinine level was reduced by 25% (p = 0.006) and the risk for development of end-stage renal disease was reduced by 28% (p = 0.006) with losartan treatment compared with placebo (Figure 3). Mean blood pressure at the end of the study was 140/74 mm Hg for the losartan group and 142/74 mm Hg for the placebo group; mean arterial pressure and pulse pressure were not significantly different between the 2 groups.
In conclusion, the ELITE II and ValHeFT trial data support the use of ARBs in addition to the standard of care in patients with heart failure who are intolerant of ACE inhibitors. The IRMA-2, IDNT, and RENAAL studies provide compelling evidence for the use of ARBs in patients with hypertension and type 2 diabetes.

20. Weber MA. The 24-hour blood pressure pattern: does it have implications for morbidity and mortality? Am J Cardiol 2002;89(suppl):27A–33A.