

# Angiotensin Receptor Blockers: Novel Role in High-Risk Patients

Usman Javed, MD<sup>a</sup>,

Prakash C. Deedwania, MD, FACC, FACP, FCCP, FAHA<sup>a,b,\*</sup>

## KEYWORDS

- Angiotensin receptor blockers • RAAS blockade
- Cardioprotection • High risk hypertension
- Diabetes mellitus

The identification of patients at high risk for cardiovascular events is imperative in the reduction of cardiovascular mortality and morbidity. Cardiovascular disease is the leading cause of death in the United States with a cardiac death occurring every 60 seconds.<sup>1</sup> Although coronary artery disease (CAD), peripheral arterial disease, cerebrovascular disease, hypertension, and diabetes mellitus (DM) contribute to risk for developing cardiovascular events, we are now faced with emerging fronts because of an increase in life expectancy and the epidemic of hypertension, obesity, metabolic syndrome, and diabetes.

The prevalence of diabetes, worldwide, is expected to increase from 2.8% in 2000 to 4.4% by the year 2030.<sup>2</sup> The lifetime risk for developing diabetes among Americans born in the year 2000 is projected at 32.8% and 38.5% for men and women, respectively.<sup>3</sup> Currently it accounts for more than 10% of total United States health care expenditure.<sup>1</sup> Cardiovascular disease is the leading cause of mortality and morbidity in patients who have diabetes, with up to 50% to 65% of patients who have diabetes dying from cardiovascular complications.<sup>4</sup>

The increase in prevalence of type 2 diabetes mellitus (T2DM) is heralded by obesity and metabolic syndrome (MS).<sup>5</sup> Recent National Health and Nutrition Examination Survey data have shown that the prevalence of people who are

overweight or obese with a body mass index (BMI) of 20 or greater increased from 56% in 1988 to 1994 to 64% in 1999 to 2000.<sup>6</sup> According to the National Cholesterol Education Program Adult Treatment Panel<sup>7</sup> MS is defined by objective clinical criteria with clustering of three or more risk factors. An increase in BMI seems to have a linear relationship with development of type II diabetes;<sup>8</sup> prevalence of T2DM is three to seven times greater in obese subjects and 20 times greater if BMI is greater than 35 kg/m<sup>2</sup>.<sup>9</sup>

Hypertension still trumps all risk factors when it comes to cardiovascular events and related morbidity.<sup>4</sup> Its relationship with target organ damage, including stroke, coronary heart disease, heart failure (HF), myocardial infarction (MI), atrial fibrillation, end-stage renal disease, peripheral vascular disease, and left ventricular hypertrophy has been well established.<sup>10</sup> Blood pressure control through antihypertensive therapy reduces stroke, MI, and HF by 20% to 40%.<sup>11</sup>

A meta-analysis involving 29 randomized trials and a total of 162,341 patients conducted by the Blood Pressure Lowering Treatment Trialists' Collaboration confirmed that angiotensin-converting enzyme inhibitors (ACEIs) provide benefits in a broad range of patients with and without hypertension.<sup>12</sup> The authors of a recent meta-analysis of 127 randomized trials concluded that the effects of renin-angiotensin system inhibition with ACEIs or

<sup>a</sup> Cardiology Section, Cardiovascular Research, UCSF Fresno Medical Education Program, UCSF School of Medicine, 2615 East Clinton Avenue (111), Fresno, CA 93703, USA

<sup>b</sup> Stanford University, Palo Alto, CA, USA

\* Corresponding author. Cardiology Section, Cardiovascular Research, UCSF Medical Education Program, UCSF School of Medicine, 2615 East Clinton Avenue (111), Fresno, CA 93703.

E-mail address: [deed1@sbcglobal.net](mailto:deed1@sbcglobal.net) (P.C. Deedwania).

angiotensin receptor blockers (ARBs) were mainly the result of lowering blood pressure, however.<sup>13</sup>

Although individual risk factor identification is important, in clinical practice most patients have multiple cardiovascular risk factors.<sup>1</sup> An increased incidence of cardiovascular events with numerous risk factors<sup>14</sup> was clearly demonstrated in the Multiple Risk Factor Intervention Trial (MRFIT).<sup>15</sup> When taken into account, the risk for cardiovascular disease increased from 24.7/10,000 person-years in patients who did not have diabetes to 77.8/10,000 person-years in high-risk patients who had diabetes with up to three risk factors.<sup>16</sup> The risk for a cardiovascular event increases considerably in patients who have a history of a prior cardiovascular event, such as CAD, peripheral arterial disease, or cerebrovascular event. Prospective data<sup>1,16</sup> have shown that up to 44% of patients who had a previous stroke can develop coronary disease or cardiac failure, whereas 20% to 46% of patients who have peripheral arterial disease are predicted to develop stroke, cardiac failure, or CAD.<sup>1</sup>

Risk factors associated with cardiovascular disease in addition to those mentioned earlier include male gender, age 45 years or older, family history of premature CAD, physical inactivity, race (ethnicity, such as African American, Hispanic, Native American, Asian American, and Pacific Islanders), impaired glucose tolerance, history of gestational diabetes and hypertension, dyslipidemia (HDL cholesterol <35 mg/dL and triglyceride >250 mg/dL), and polycystic ovary syndrome.<sup>14</sup>

As the paradigm has shifted toward the identification of the high-risk state for future cardiovascular events and their treatment, clinical practice and pharmacotherapy have evolved a better understanding of the underlying pathophysiology and the need for an aggressive preventive strategy in this high-risk population. It includes prevention and control of traditional risk factors, such as hypertension and diabetes, with lifestyle changes and therapeutic intervention. Because hypertension remains the most prevalent of all risk factors, a variety of antihypertensive agents have been used.<sup>11,17</sup> Patients who have uncomplicated hypertension or those who have no specific indication for a particular antihypertensive agent are recommended to be treated with a diuretic agent for control of their blood pressure. Beta-blockers are no longer used as a primary or secondary antihypertensive agent in patients who do not have a specific indication for these drugs because of worsening glycemic control and an unfavorable impact on the risk for stroke (especially with atenolol), particularly in elderly patients. Recent data emphasize the beneficial role of renin-angiotensin-

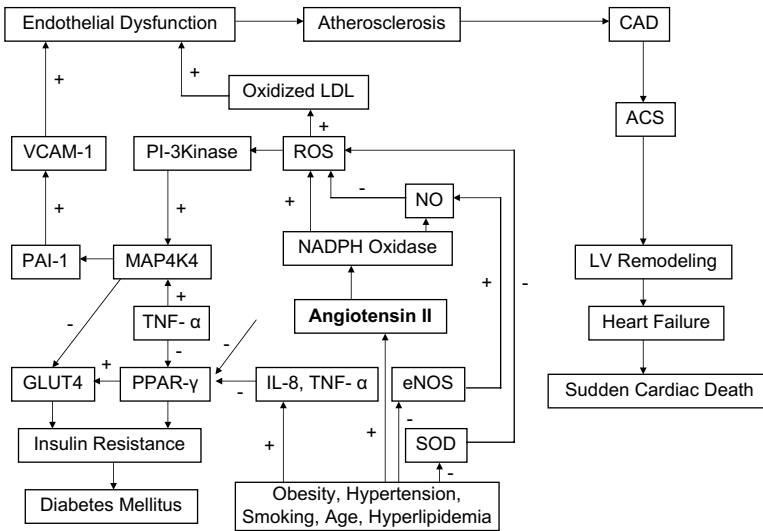
aldosterone system (RAAS) blockers, including ACEIs and ARBs, because of their favorable cardiovascular outcomes.<sup>18</sup> ARBs or ACEIs, alone or in combination when used in high-risk patients, not only control blood pressure but also have shown cardiovascular benefit beyond blood pressure control.<sup>19–21</sup> This article addresses the role of RAAS activation in the high-risk metabolic milieu and the role of ARBs in targeting and inhibiting the RAAS for cardiovascular protection.

### IMPORTANCE OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM PATHWAY AND SIGNIFICANCE OF ANGIOTENSIN RECEPTOR TYPE I

It is now well established that the activation of the RAAS plays a critical role in the initiation and progression of hypertension, diabetes, vascular remodeling, and cardiovascular changes leading to target organ damage.<sup>22</sup> Several experimental and clinical studies have shown that RAAS blockade results in a paramount yet multifaceted effect with benefits beyond control of hypertension including reduction of new-onset T2DM, prevention of progression of nephropathy to renal failure, and modulation of signaling pathways involved in cardiovascular cascade contributing to the increased cardiovascular events.<sup>23–26</sup>

The RAAS is an in-step neuroendocrine cascade that controls cardiovascular, renal, adrenal, and sympathetic function by numerous mechanisms, including control of body fluid and electrolyte balance. Angiotensin II (ang II) is the primary mediator of the RAAS that elicits a wide range of effects through angiotensin II type 1 (AT1) receptor. These include vasoconstriction, sodium and water retention, and sympathetic activation leading to hypertension and vascular and cardiac remodeling, which if uninterrupted can lead to HF. Angiotensin II (ang II) formation occurs from angiotensinogen through a series of steps.<sup>27</sup> Renin, which is secreted by the juxtaglomerular apparatus in the kidney, catalyzes the conversion of angiotensinogen to angiotensin I (ang I). Ang I is subsequently converted to ang II by ACE. ACE-induced conversion accounts for about 60% of ang II. Alternate pathways also exist that convert angiotensinogen directly to angiotensin II. These include serine proteinases, such as chymase and cathepsin G, and tissue plasminogen activator-dependent pathways that contribute to significant production of ang II in diseased vessels and heart (eg, post-MI).<sup>28,29</sup>

Angiotensin II mediates its effects by acting on AT1 and type II (AT2) receptors (**Fig. 1**). AT1 receptors are widespread throughout the tissues and lead to deleterious effects, which include vasoconstriction, aldosterone release, increased sodium



**Fig. 1.** Clinico-pathological sequelae associated with angiotensin II type I receptor overexpression. ACS, acute coronary syndrome; CAD, coronary artery disease; eNOS, endothelial nitric oxide synthase; GLUT, glucose uptake transporter; IL-1, interleukin; LDL, low density lipoprotein; MAP4K4, mitogen-activated protein kinase; NADPH, nicotinamide adenine dinucleotide phosphatase; NO, nitric oxide; PAI-1, plasminogen activator inhibitor; PI-3, phosphatidylinositol-3; PPAR, peroxisome proliferator-activated receptor; ROS, reactive oxygen species; SOD, superoxide dismutase; TNF, tumor necrosis factor; VCAM-1, vascular cell adhesion molecule.

retention, and cellular hypertrophy of vessel wall and myocardium. The genomic effects of ATI result from an enhanced intracellular activation of transcription factors, such as nuclear factor- $\kappa$ B and activator protein 1, monocyte chemoattractant protein-1 (MCP-1), vascular cell adhesion molecule, plasminogen activator inhibitor, and the release of the cytokines interleukin-6 (IL-6) and tumor necrosis factor (TNF- $\alpha$ ). The result is an increased oxidative stress and level of transforming growth factor (TGF) leading to a proinflammatory, atherogenic, and prothrombotic environment.<sup>30–35</sup> The function of the AT2 receptor, which is up-regulated in response to tissue injury, is not well understood but seems to mediate beneficial effects that include vasodilatation, inhibition of cell growth and proliferation, and cell differentiation. While blocking the AT1 receptor, most ARBs have an intrinsic AT2 receptor-stimulating property attributable to increased levels of ang II secondary to the RAAS feedback loop. Valsartan has been shown to reduce cardiac remodeling, coronary arterial thickness, and perivascular fibrosis by way of AT2 receptor stimulation. In vitro studies have also demonstrated that the renin, ACE, and AT1 receptor genes are significantly up-regulated in obese patients who have hypertension, which might explain the high risk for cardiovascular disease in these patients.<sup>25–36</sup>

The cardiovascular risk factors, such as diabetes, smoking, and dyslipidemia, increase the levels of ang II, which in turn might trigger the progression to atherosclerosis plaque destabilization, left ventricular hypertrophy, cardiac apoptosis, and increased arrhythmogenicity.<sup>31</sup> The net result

is the loss of cardiac muscle mass, left ventricle remodeling, progressing to HF, end-stage cardiomyopathy, and increased risk for sudden cardiac death.

#### RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM INHIBITION AND CARDIOVASCULAR PROTECTION

RAAS blockade has beneficial effects on inflammation, oxidative stress, and endothelial function. RAAS blockade attenuates hyperglycemia-induced endothelial dysfunction and reduces the release of proinflammatory cytokines that may mediate the development of cardiovascular disease in high-risk patients who have diabetes.<sup>37</sup> Lisinopril has been shown to reduce cardiovascular oxidative stress, cardiomyocyte hypertrophy, and loss of cardiac function in rats with streptozotocin-induced diabetes and preserve the elastin/collagen ratio in the aorta media (changes that are often associated with diabetes).<sup>38</sup>

Blockade of RAAS promotes insulin sensitivity by increasing the differentiation of preadipocytes and promoting the recruitment of preadipocytes. The result is an increase in small insulin-sensitive adipocytes, followed by a redistribution of lipids to adipose tissue and improved insulin sensitivity. In a fructose-fed rat model of metabolic syndrome, RAAS blockade with temocapril or olmesartan showed a significant improvement in insulin sensitivity and blood pressure and decrease in adipocyte size. This finding was later confirmed by in vitro study in primary cultured human preadipocytes that demonstrated inhibition of adipocyte differentiation with angiotensin II.<sup>39–41</sup>

Several small observational studies have shown an improvement in flow-mediated vasodilatation in patients who had hypertension, diabetes, and CAD associated with RAAS inhibition by ARBs. It is postulated to be mediated by increased production of endothelium-derived nitric oxide (NO) production. Beneficial effects of ARBs, such as increased superoxide dismutase activity and endothelial NO synthase activity, reduced vasoconstriction, and decreased blood pressure, may also contribute to improvement in endothelial function through increase in NO release and inhibition of NO degradation.<sup>31</sup> Further randomized controlled studies are needed to confirm the reduction of outcomes associated with improved endothelial function.

#### **RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM AS A THERAPEUTIC TARGET IN HIGH-RISK PATIENTS: THE ROLE OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS**

Although ACEIs were initially developed for treatment of hypertension, their use has been extended to HF, post-MI, and renal disease. In addition, ACEIs seem to have pleiotropic effects as documented by their vasodilating, anti-inflammatory, plaque stabilizing, antithrombotic, and antiproliferative properties. The net result is that their therapeutic effects go beyond blood pressure control leading to beneficial effects on vascular and cardiac remodeling, reduced incidence of diabetes, renal protection, and cerebral and cardiovascular protection. These properties of ACEIs have led to their use in primary and secondary prevention for cardiovascular disease.

Several clinical trials evaluating the efficacy of RAAS blockade with ACEIs or ARBs demonstrated reductions in new-onset diabetes and cardiovascular event rates following treatment with these agents. The Captopril Prevention Project (CAPPP) was a landmark trial that evaluated the effectiveness of captopril to reduce cardiovascular mortality and morbidity in more than 10,000 hypertensive patients. A subanalysis of CAPPP revealed that hypertensive patients who had diabetes receiving captopril had a 66% lower rate of fatal and nonfatal MI compared with conventional therapy with diuretics or beta-blockers ( $P = .002$ ). Overall, fatal cardiovascular events were reduced by about 50% in patients receiving captopril compared with conventional therapy.<sup>42</sup>

The Heart Outcomes Prevention Evaluation (HOPE) was a pivotal study and a trendsetter in our current practice of cardiovascular medicine. During a 4.5-year follow-up, treatment with ramipril demonstrated significant reduction in

cardiovascular events, mortality, and new-onset diabetes in high-risk patients.<sup>43</sup> The cardiovascular benefits of ramipril were unrelenting in the 2.6-year extension of the study, HOPE–The Ongoing Outcomes (HOPE-TOO).<sup>44</sup> Overall, during the 7.2 years of follow-up, patients receiving ramipril had a 3.6% absolute risk reduction in combined incidence of MI, stroke, and cardiovascular death compared with the placebo group ( $P = .0002$ ); and 31% relative risk reduction (RRR) of new-onset DM in patients taking ramipril ( $P = .0006$ ). Although it is somewhat debatable, the investigators concluded that cardiovascular protective effects of ramipril were primarily not related to their antihypertensive effects.

The European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA) extended the results seen in the HOPE trial.<sup>45</sup> In a large, well-treated patient population of stable CAD, perindopril showed a clear reduction in cardiovascular events and mortality versus placebo (8% versus 9.9%,  $P < .0003$ ). The cardiovascular benefits of perindopril seemed to be beyond its antihypertensive properties because the drop in blood pressure was modest (5 versus 2 mmHg).

#### **RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM AS A THERAPEUTIC TARGET IN HIGH RISK PATIENTS: THE ROLE OF ANGIOTENSIN RECEPTOR BLOCKERS**

ARBs act by selectively blocking the binding of ang II to the AT1 receptor but not the AT2 receptor. ARBs have been shown to improve insulin-mediated glucose uptake, improve endothelial function, increase nitric oxide activation, reduce inflammatory response, and increase bradykinin levels (**Box 1**). Although many of these pleiotropic effect of ARBs have been well demonstrated in animal models, similar effect are yet to be established in human clinical studies.

#### **ROLE OF ANGIOTENSIN RECEPTOR BLOCKERS IN ENDOTHELIAL IMPROVEMENT**

ACEIs have already demonstrated their protective effects on cardiovascular, neurologic, and renal complications in high-risk patients. Better understanding of RAAS led to the realization that ACE inhibitors do not always provide complete blockade, however. As much as 40% of ang II formation occurs from alternative pathways leading to the concept described as ACE escape. Moreover, ACE inhibitors are not well tolerated in a significant fraction of patients because of associated angioedema and cough. Hence ARBs have emerged as an alternative and a potential adjunct to the ACEIs.

**Box 1****Metabolic effects of angiotensin receptor blockers**

Promote differentiation of adipocytes  
 Increase adipocyte uptake of glucose and lipid  
 Decrease glycogenolysis  
 Inhibit secretion of triglycerides into the circulation  
 Increase vasodilatation  
 Increase delivery of glucose and insulin to skeletal muscle  
 Inhibit apoptosis in pancreas  
 Decrease catecholamine release

ARBs are more selective than ACEIs in that they selectively antagonize AT1 receptors. A theoretic advantage of ARBs is that non-ACE sources of ang II are unable to activate AT1. Blockade of AT1 interrupts the negative feedback loop and increases circulating ang II levels. The result is unopposed AT2 stimulation because of heightened ang II levels resulting in vasodilatation and other beneficial effects. Despite these favorable effects of ARBs, an absolute effectiveness of benefits from this class of medication compared with the ACEIs is yet to be established, particularly in high-risk individuals.<sup>22,27</sup>

ARBs, like ACEIs, have an effect on the regulation of endothelial function. Ang II plays a significant role in endothelial dysfunction in general and in patients who have diabetes in particular. Insulin binds to tyrosine kinase, which leads to autophosphorylation of tyrosine residue turning on the insulin-signaling pathways, which enhances uptake of glucose by skeletal muscle. The second activated pathway is the mitogen-activated protein kinase, which promotes vascular smooth muscle cell proliferation and migration induced by insulin, thrombin, and platelet-derived growth factors. A third pathway is triggered that leads to activation of P70 S6 kinase, a regulator of protein synthesis.<sup>45,46</sup>

In animal models, valsartan has shown a reduction in the expression of proinflammatory markers, such as MCP-1, TNF, IL-6, and IL-1, and it inhibits migration of inflammatory cells into the injured arteries. Losartan has shown a decrease in reactive oxidants, increased NO production, and improved flow-mediated vasodilatation.<sup>47-49</sup> In humans, ARB treatment in patients who have essential hypertension decreases peripheral vascular resistance and radial arterial thickness and reduces left ventricular muscle mass.<sup>50</sup> These beneficial effects of ARBs have the potential to

provide cardiovascular protection, especially in high-risk individuals.

### CLINICAL STUDIES OF ANGIOTENSIN RECEPTOR BLOCKERS IN VARIOUS HIGH-RISK GROUPS

Several important questions remain concerning the role of RAAS inhibition and target end-organ protection. An intervention for lowering blood pressure alone reduces the progression of vascular and renal disease in high-risk patients. These individuals must be identified, however. Based on the results of several clinical trials, including HOPE, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack trial, and the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) trial, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) identified renal disease and diabetes as compelling indications for the use of more aggressive blood pressure (BP)-lowering treatment.<sup>44,50-53</sup> Also, in recognition of cardiovascular risk associated with BP elevation, JNC 7 categorized individuals who have systolic BP ranging from 120 to 139 mm Hg and diastolic BP ranging from 90 to 99 mm Hg as "prehypertensive." Although no pharmacologic intervention was recommended for the management of prehypertension, the stated expectation was that greater attention would be paid to nonpharmacologic approaches and lifestyle modification and an early recognition and intervention for a higher risk. Risk is set forth by the traditional factors described earlier; nonetheless, hypertension remains the most sensitive predictor of target organ damage.

The Trial of Preventing Hypertension (TROPHY) was a study designed to look at the implications of an early pharmacologic treatment with candesartan (an ARB) of prehypertension in preventing the development of hypertension. During the first 2 years, hypertension developed in 40.4% of subjects in the placebo group compared with only 13.6% of those in the candesartan group for a RRR of 66.3% ( $P < .0001$ ). At 4 years, hypertension had developed in 63.0% in the placebo group versus 53.2% in the candesartan group (RRR 15.6%;  $P < .0069$ ). The relative proportion of participants who were hypertension-free was 26.5% greater in the candesartan group.<sup>54</sup>

### ANGIOTENSIN RECEPTOR BLOCKERS IN HIGH-RISK HYPERTENSIVES

LIFE was one of the initial clinical trials that compared the efficacy of an ARB in a high-risk

population with evidence of target organ damage (left ventricular hypertrophy).<sup>52</sup> In patients who had advanced hypertension and left ventricular hypertrophy, losartan in comparison with atenolol showed reduction in composite cardiovascular mortality, MI, and stroke (11% losartan versus 13% atenolol, relative risk [RR] = 0.13;  $P = .021$ ). The benefit was largely derived from the reduction in stroke (losartan 5% versus atenolol 7%). In the subgroup analysis of patients who did not have vascular disease, losartan reduced the primary composite endpoint of cardiovascular morbidity and mortality along with stroke (HR 0.18,  $P = .008$ ). These beneficial effects of losartan were most evident in the diabetic subgroup. In the analysis of patients who had diabetes, losartan did reduce primary composite endpoint, cardiovascular mortality, and HF hospitalizations compared with atenolol (hazard ratio [HR] 0.77,  $P = .031$ ), and mortality (HR 0.62,  $P = .002$ ). In patients who had isolated systolic hypertension in the LIFE study, losartan reduced all-cause mortality (HR 0.72,  $P = .05$ ) but failed to show a significant reduction in the primary composite endpoint of cardiovascular mortality and stroke compared with atenolol. In another subgroup analysis of the LIFE trial, losartan versus atenolol revealed that there was actually an increased risk for stroke, 8.9% versus 4.6% for African American patients (adjusted HR 2.18,  $P = .03$ ). African American women derive similar benefit from ARBs as men. The subgroup of African American patients who had DM on losartan had a reduction in cardiovascular mortality but not a significant decrease in stroke.

Various other studies have evaluated the effects of ARBs on all-cause or cardiovascular mortality and morbidity in patients who have high cardiovascular risk (**Table 1**). The Morbidity and Mortality after Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention (MOSES) trial compared morbidity and mortality in treatment with eprosartan or nitrendipine.<sup>55</sup> The combined primary endpoint of all-cause mortality, and cardiovascular and cerebrovascular events in patients who had hypertension and history of stroke was compared with nitrendipine. The combined primary endpoint was significantly reduced with eprosartan compared with nitrendipine, with an incidence density of 13.25% versus 16.71%, respectively, and an incidence ratio (IDR) of 0.79 (95% CI 0.66–0.96;  $P = .014$ ). The incidence was also significantly reduced with eprosartan for fatal and nonfatal stroke (IDR 0.75, 95% CI 0.55–0.97;  $P = .025$ ). This difference in the primary outcome is seen despite similar reduction in blood pressure in the two treatment groups. This trial also

revealed that patients treated with eprosartan had significantly fewer cerebrovascular events compared with patients treated with nitrendipine.

The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) study compared valsartan to the amlodipine in patients who had hypertension and high cardiovascular risk.<sup>56</sup> This large, multicenter, randomized trial enrolled 15,245 patients who had treated or untreated hypertension who were at high risk for cardiac events. During the mean follow-up of 4.2 years, there was no difference in all-cause mortality between the two groups (11.0% for valsartan, 10.8% for amlodipine; HR 1.04, 95% CI 0.94–1.14;  $P = .45\%$ ). Overall cardiac mortality was similar but fatal and nonfatal MI reached significance (4.8% versus 4.1%, adjusted HR 1.19, 95% CI 1.02–1.38,  $P = .02$ ).

ARBs have also been shown to be beneficial in improving chronic cerebral ischemia. Administration of candesartan has been shown to improve cerebral artery media thickness, improve cerebral blood flow, and reduce the expression of c-Fos and c-Jun proteins in the brain that are associated with chronic neurodegenerative diseases.<sup>57</sup> Recent studies suggest that RAAS blockade may also reduce the incidence of cerebrovascular events in high-risk groups; for example, the risk for stroke was reduced with ramipril in the HOPE trial, which also included patients who had prior transient ischemic attack (TIA) or stroke.<sup>43</sup>

### ANGIOTENSIN RECEPTOR BLOCKERS IN POST-MYOCARDIAL INFARCTION PATIENTS

Although there have been no head-to-head or placebo-controlled trials evaluating the effects of ARBs in patients who have had a recent MI, ARBs are often used in clinical practice to prevent the development or progression of HF and to reduce mortality in such patients irrespective of the presence of HF. This use is largely extrapolated from two clinical trials of ARB in post-MI patients (**Table 2**).

The Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL) compared losartan with captopril in patients who had post-MI HF.<sup>58</sup> It failed to show non-inferiority of losartan to captopril in reducing all-cause mortality in patients. In the intent-to-treat analysis, the upper one-sided 95% confidence boundary for the relative risk for death from any cause was 1.28, which did not satisfy the non-inferiority criterion (upper boundary 1.10). Also, significantly fewer cardiovascular deaths and sudden cardiac deaths were observed in the captopril group. There was no difference in the incidence of MI. Consistent with previous trials, losartan was

Table 1 Clinical studies of angiotensin receptor blockers in hypertension						
Trial	Condition	n	Follow-up	ARB	Outcome	Results
TROPHY	Prehypertension	809	4 y	Candesartan versus placebo for 2 y, followed by no therapy	Hypertension	66.3% RRR at 2 y and 15.6% RRR at 4 y
LIFE	Hypertension	9,193	5 y	Losartan versus atenolol	Composite, CV death, stroke, MI	13% RRR
VALUE	Hypertension	15,245	4.2 y	Valsartan versus amlodipine	Composite endpoint	No difference
SCOPE	Hypertension, elderly	4,964	3.7 y	Candesartan versus diuretic versus beta-blocker	Composite, CV death, nonfatal MI, and non fatal stroke	No difference in composite endpoint, 28% RRR in nonfatal stroke
MOSES	Hypertension, stroke	1,405	2.5 y	Eprosartan versus nitrendipine	Composite, all-cause mortality, CV, and cerebrovascular	IDR for composite endpoints 0.79 ( $P = .014$ ), for stroke 0.75 ( $P = .03$ )

*Abbreviations:* CV, cardiovascular; IDR, incidence ratio; MOSES, Morbidity and Mortality after Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention trial; SCOPE, The Study on Cognition and Prognosis in the Elderly; VALUE, Valsartan Antihypertensive Long-term Use Evaluation.

<b>Trial</b>	<b>Condition</b>	<b>n</b>	<b>Follow-up</b>	<b>ARB</b>	<b>Outcome</b>	<b>Results</b>
OPTIMAAL	Acute MI and HF	5,477	6 mo	Losartan versus captopril	All-cause mortality, nonfatal MI, SCD	No difference, ↑ mortality with losartan
VALIANT	Acute MI and HF	14,703	2.1 y	Valsartan versus captopril or both	All-cause mortality, CV death, MI & CHF hospitalization	No difference
ValHeFT	CHF	5,010	4 y	Valsartan versus placebo	All-cause mortality	No change in mortality, ↓ hospitalization
ELITE II	CHF	3,152	1.6 y	Losartan versus captopril	Composite	No difference
CHARM-Added	CHF	2,548	3.4 y	Candesartan versus placebo	Composite	15% RRR
CHARM-Alternate	CHF	2,028	2.8 y	Candesartan versus placebo	Composite	23% RRR
CHARM-Preserved	CHF	3,023	3 y	Candesartan versus placebo	CV death	11% RRR
CHARM overall	CHF	7,601	2 y	Candesartan versus placebo	All-cause mortality	17% RRR
ONTARGET	CAD, diabetes, hypertension	25,620	4.8 y	Telmisartan versus ramipril or both	Composite, CV death, stroke, MI, hospitalization	Non-inferiority to ramipril, ↑ adverse effects with combination

*Abbreviations:* CHARM, Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity; CHF, congestive heart failure; ELITE, Evaluation of Losartan in the Elderly trial; ONTARGET, Telmisartan Alone and in combination with Ramipril Global Endpoint Trial; OPTIMAAL, Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan; SCD, sudden cardiac death; ValHeFT, Valsartan Heart Failure Trial; VALIANT, Valsartan In Acute Myocardial Infarction Trial.



better tolerated than captopril, with fewer patients discontinuing study medication for any reason.

In the Valsartan In Acute Myocardial Infarction Trial (VALIANT), valsartan was shown to be as effective as captopril in reducing all-cause mortality and morbidity in patients who had recent MI and were at high risk for further coronary events ( $P = .004$ ). After a mean follow-up of 24.7 months, survival was similar in the valsartan, valsartan and captopril, and captopril monotherapy groups.<sup>59</sup> The non-inferiority analysis confirmed that valsartan was no less effective than captopril. Likewise, the secondary endpoint of cardiovascular death, MI, or hospitalization for HF was similar in the three groups (Fig. 2). Captopril and valsartan were equally well tolerated. Cough, taste disturbance, and rash were more common with captopril, whereas hypotension and renal dysfunction were more common in the valsartan group. The combination of valsartan and captopril did not provide any advantage over monotherapy with either and it was poorly tolerated and had higher discontinuation rate. Based on the results of the VALIANT, valsartan is now approved for use in post-MI setting.

**ANGIOTENSIN RECEPTOR BLOCKERS IN HEART FAILURE**

Although treatment with ACEIs is now well established as first-line therapy for all patients who

have HF, it is also recognized that some patients may not tolerate ACEIs and others might still be symptomatic despite optimal doses of ACEIs. It has been postulated that ARBs can be a suitable alternative and can provide additional benefits because of blockade of ang II produced by the alternate pathway. There is now good evidence that valsartan and candesartan are beneficial in patients who have HF who are unable to tolerate therapy with an ACEI. This evidence is based on evaluation of treatment with ARBs in several large clinical trials in patients who had HF (see Table 2).

The Evaluation of Losartan in the Elderly trial (ELITE II) was designed to compare the effects of losartan with those of captopril on mortality, morbidity, safety, and tolerability in patients who have symptomatic HF (New York Heart Association [NYHA] class II–III, mean left ventricular ejection fraction [LVEF] <35%).<sup>60</sup> In this high-risk cohort, 60% percent had a history of MI, 50% had hypertension, and about one third had atrial fibrillation. On analysis, a 13% reduction in mortality was observed in patients treated with captopril. There was no difference in hospitalizations ( $P = .45$ ). Losartan was better tolerated than captopril because of more frequent cough in the captopril arm. Because ELITE II was a superiority trial and losartan was not superior to captopril, it remains unclear whether losartan is more effective in this setting. A major critique of the study

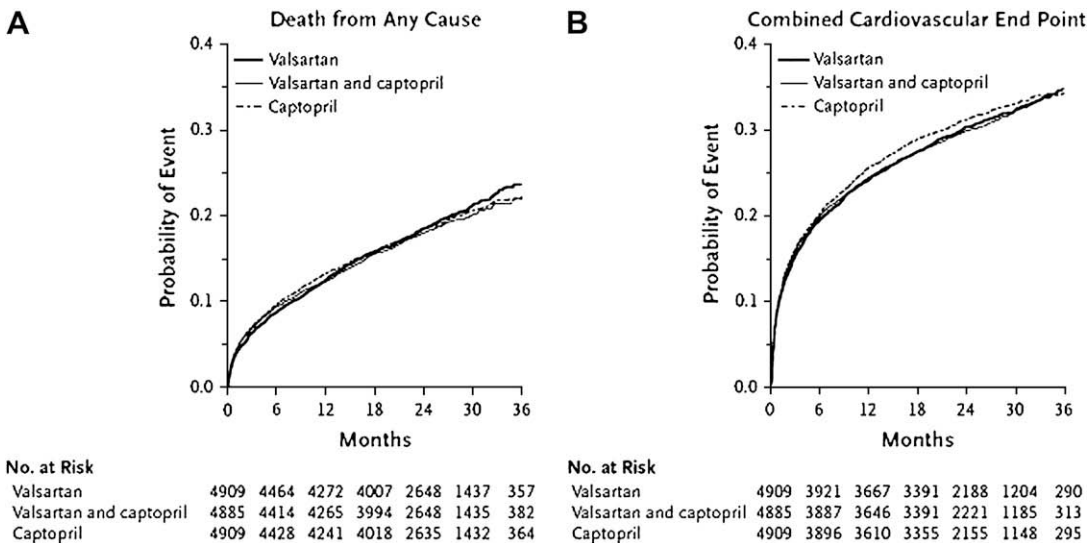


Fig. 2. Kaplan-Meier estimates of the rate of death from any cause (A) and the rate of death from cardiovascular causes, reinfarction, or hospitalization for HF (B), according to treatment group. (From Pfeffer MA, McMurray JJV, Velazquez EJ, et al, for the Valsartan in Acute Myocardial Infarction Trial Investigators. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003;349:1898; with permission. Copyright © 2003, Massachusetts Medical Society.)

is the lower dose of losartan (50 mg/d) that is believed to be insufficient compared with captopril (150 mg/d).

In the Valsartan Heart Failure Trial (ValHeFT), valsartan was evaluated in patients who had a history of HF (NYHA class II–IV) and an ejection fraction less than 40% who were still symptomatic on standard therapy with diuretic, digoxin, and ACEI.<sup>61</sup> The co-primary outcomes were mortality and the combined endpoint of mortality and morbidity. Patients were assigned to receive valsartan or placebo in addition to background therapy, including ACEIs in 93%. There was no difference in mortality between the two groups. A subgroup analysis revealed that patients not receiving an ACE inhibitor at baseline (7.3%,  $n = 366$ ) derived the greatest benefit from valsartan with a 44% reduction in the combined endpoint of mortality and morbidity. Significantly more patients receiving valsartan discontinued therapy (9.9% versus 7.2%;  $P < .001$ ) because of common adverse effects. Subgroup analysis from ValHeFT suggested that an ARB might be appropriate in patients unable to tolerate an ACEI, but also raised questions about the safety of the combination of an ACEI,  $\beta$ -blocker, and ARB.

The Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) trial compared candesartan with enalapril or the combination of candesartan and enalapril.<sup>62</sup> Primary outcomes included the distance on 6-minute walk, ventricular function as assessed by ejection fraction, end-diastolic and end-systolic volumes, blood pressure, quality of life, and levels of aldosterone and brain natriuretic peptide. Over a 43-week follow-up, this study showed that candesartan and enalapril resulted in similar improvements in exercise tolerance, ventricular function, NYHA functional class, and quality of life. In addition, blood pressure, aldosterone, and brain natriuretic peptide levels decreased significantly more in the combination therapy group. Candesartan and enalapril were found equally effective with respect to the primary endpoints and tolerability.

The Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program had three parallel, independent, integrated, and randomized, double-blind, placebo-controlled clinical trials comparing candesartan with placebo in patients who had symptomatic HF.<sup>63</sup> The primary endpoint for each arm was to determine whether candesartan would reduce the risk for cardiovascular death or hospital admission for HF compared with standard therapy alone. CHARM-Alternative<sup>64</sup> is important because it compared candesartan with placebo in patients

who had left ventricular dysfunction and a history of intolerance to ACEIs. The most common reason for ACEI intolerance was cough, accounting for more than 70% of subjects, whereas 4% of patients had documented angioedema. A total of 59% of patients treated with candesartan and 73% of the placebo group reached the target dose. In the candesartan group, 334 patients had primary endpoints (cardiovascular death and hospitalization for HF) versus 406 patients in the placebo group (RRR 23%,  $P = .0004$ ). There was no statistically significant difference in cardiovascular or total mortality. Hospital admissions for worsening HF were reduced by 32% ( $P < .0001$ ) in patients treated with candesartan. Candesartan was discontinued more often than placebo for renal dysfunction, hyperkalemia, and hypotension. Results from CHARM-Alternative study suggest that patients who cannot tolerate an ACEI should be treated with candesartan, with the prospect of reduction in HF decompensation but not in mortality and risk for MI.

CHARM-Preserved<sup>65</sup> was the second arm that enrolled patients who had HF with preserved LVEF (>40%). Sixty percent of patients in each group had NYHA class II symptoms and nearly 40% had class III symptoms. Subjects had a higher number of underlying risks for cardiovascular events: hypertension in 65%, MI in 45%, diabetes and angina in 27%, and stroke in 9%. The primary outcome, including MI, cardiovascular death, and noncardiovascular death, was similar in the two treatment groups. Hospitalization for HF was lower in the candesartan group than in the placebo group but overall admissions were similar ( $P = .79$ ). In a high-risk population of patients who had presumed diastolic HF, candesartan reduced hospital admission for HF but did not attenuate mortality, MI, or total hospital admissions.

The results of the CHARM-Added<sup>66</sup> study suggested that adding candesartan at the relatively high mean dose of 24 mg on top of standard therapy with a beta-blocker and an ACEI in NYHA HF class II–III patients who have reduced LVEF reduces cardiovascular mortality by 17% and HF hospitalization by 17%. Overall, in the CHARM program, the mortality rate was 23% in candesartan group and 25% in patients receiving placebo ( $P = .032$ ). Fewer cardiovascular deaths and hospital admissions for congestive heart failure (CHF) were observed in the candesartan group. Pooled analyses of the CHARM studies demonstrated that RRR of mortality was 12% with candesartan. The composite outcome of cardiovascular death and nonfatal MI was reduced by 13% ( $P = .012$ ).

## ANGIOTENSIN RECEPTOR BLOCKERS IN NEPHROPATHY

The renoprotective effect of the ARBs is the constellation of improved renal blood flow and endothelial function, usually by reducing intraglomerular pressure and preserving NO activity. This finding has been confirmed in animal and human studies. In rat models, the use of valsartan reduced albuminuria and chronic allograft rejection. AT1 receptor blockade leads to an increase in circulating ang II, which stimulates the unblocked AT2 receptor. The result is pressure natriuresis and vasodilatation because of an increased NO and bradykinin production.

The role of the renin-angiotensin axis and its interaction with endothelium and insulin-signaling pathways seems to have potential in prevention of diabetes and end-stage renal disease in using agents that block the RAAS. Clinical trials have shown the effects of ARBs on renal disease progression in high-risk patients (Table 3). ARBs reduce or eliminate microalbuminuria, an early sign of renal damage. The benefit of ARB therapy has also been demonstrated in patients who have nondiabetic nephropathy.

In the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study,<sup>67</sup> losartan compared with placebo significantly reduced serum creatinine, end-stage renal disease, and death in patients who had diabetic nephropathy (RR = 0.84;  $P = .02$ , number needed to treat [NNT] = 28). A new subgroup analysis of most cardiovascular outcomes showed no significant differences, but favored irbesartan over placebo for HF ( $P = .048$ ).

In two other studies, irbesartan was studied in patients who had diabetic nephropathy. In the Irbesartan in Diabetic Nephropathy Trial (IDNT),<sup>68</sup> when compared with amlodipine irbesartan showed significant reduction of overt proteinuria, end-stage renal disease, and doubling of serum creatinine (RR = 0.80,  $P = .02$ , NNT = 16). In the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria trial (IRMA),<sup>69</sup> therapy with 150 mg or 300 mg of irbesartan was compared with placebo. The primary endpoint of the study was the onset of overt nephropathy, which was defined as urinary albumin excretion rate greater than 200  $\mu\text{g}/\text{min}$  and at least 30% higher than baseline. Irbesartan showed RRR of 44% and 68% (150 mg and 300 mg of irbesartan, respectively) versus conventional therapy.

The Combination Treatment of Angiotensin II Receptor Blocker and Angiotensin-Converting Enzyme Inhibitor in Nondiabetic Renal Disease (COOPERATE)<sup>70</sup> study evaluated the combination

of losartan and trandolapril in patients who had nondiabetic nephropathy and showed significant reduction in composite endpoint of doubling of the serum creatinine or end-stage renal disease compared with either treatment alone (RRR 62% and 60% for losartan and trandolapril, respectively). These results not only emphasize the role of ARB in nondiabetic nephropathy but also demonstrate the benefit of combination therapy with ACEIs and ARBs. In the Irbesartan in the Management of Proteinuric Patients at High Risk for Vascular Events trial (IMPROVE),<sup>71</sup> combination of ramipril and irbesartan compared with ramipril showed a greater reduction in onset of overt proteinuria but did not achieve statistical significance (46% versus 42%,  $P$  not significant). This finding has led to the suggestion of using monotherapy with RAAS blockers in early-stage renal disease and relatively low albumin excretion, and combination therapy in patients who have heavier proteinuria who have failed monotherapy.

## PREVENTION OF DIABETES MELLITUS WITH ANGIOTENSIN RECEPTOR BLOCKERS *Pathophysiologic Basis*

In obese patients who are diabetic, there is a potential inhibition of the differentiation of the human preadipocytes into mature adipocytes. This inhibition is in part attributable to an up-regulation of angiotensinogen and angiotensin II receptor overexpression in the adipose tissue.<sup>72-74</sup> This phenomenon is supported by the promotion of preadipocyte differentiation *in vitro* by the ARBs. An overexpression of angiotensin receptors in obesity leads to inhibition of peroxisome proliferator-activated receptor (PPAR)- $\gamma$  activity, which might lead to insulin resistance.<sup>73-75</sup> Activation of this nuclear receptor might have a significant role in diabetes prevention. Irbesartan and telmisartan have been shown to enhance PPAR- $\gamma$  activation *in vitro* and to increase adiponectin secretion by adipocytes, both of which might result in improved insulin sensitivity and lead to prevention of diabetes and atherogenicity.<sup>76,77</sup> BMI has been shown to have a positive correlation with increasing circulating plasma ang II and TNF- $\alpha$  levels. A positive relation has also been demonstrated between hyperinsulinemia, TNF- $\alpha$  levels, and ang II secretion from the adipose tissue. Higher levels of circulating ang II are known to be associated with hypertension and hyperinsulinemia. They are also considered a proinflammatory factor, leading to expression of inflammatory genes in vascular smooth muscle cells.<sup>78,79</sup>

**Table 3**  
Clinical studies of angiotensin receptor blockers in coronary heart disease and heart failure

Trial	Condition	n	Follow-up	ARB	Outcome	Results
DETAIL	T2DM	250	5 y	Telmisartan versus enalapril	Decline in GFR; ESRD; all cause mortality	Non-inferiority to enalapril
CALM	HTN, T2DM, microalbuminuria	199	3 mo	Candesartan, lisinopril or both	Change in BP and UA/Cr	Combination: decrease in BP and UA/Cr > versus candesartan or lisinopril
IMPROVE	HTN, microalbuminuria	405	5 mo	Irbesartan, ramipril, or both	Reduction in urine albumin excretion	Combination 46% ↓; ramipril 42% ↓ (P not significant)
COOPERATE	Nondiabetic nephropathy	263	2.9 y	Losartan, trandolapril, or both	Time to doubling of serum creatinine, ESRD	RRR 62% combination versus trandolapril; 60% versus losartan
IRMA-2	Diabetic nephropathy	590	3 mo	Irbesartan versus placebo	Albuminuria, overt proteinuria	24% ↓ with 150 mg and 38% with 300 mg, 70% ↓ in proteinuria
IDNT	Diabetic nephropathy	1715	2.6 y	Irbesartan versus amlodipine versus placebo	ESRD, doubling of serum creatinine	23% RRR versus placebo, 20% versus amlodipine
RENAAL	Diabetic nephropathy	1513	3.4 y	Losartan versus placebo	Composite, ESRD, 2X serum creatinine, death	16% RRR composite, 25% ↓ in 2X serum creatinine, no change in death
MARVAL	Diabetic nephropathy, HTN	332	6 mo	Valsartan versus amlodipine	Urinary albumin excretion rate	29.6% ↓ with valsartan versus 17.2%, ↑ with amlodipine

*Abbreviations:* CALM, Candesartan And Lisinopril Microalbuminuria trial; COOPERATE, Combination Treatment of Angiotensin II Receptor Blocker and Angiotensin-Converting Enzyme Inhibitor in Nondiabetic Renal Disease Trial; DETAIL, Diabetics Exposed to Telmisartan and Enalapril; ESRD, end-stage renal disease; GFR, glomerular filtration rate; HTN, hypertension; IDNT, Irbesartan in Diabetic Nephropathy Trial; IMPROVE, Irbesartan in the Management of Proteinuric Patients at High Risk for Vascular Events trial; IRMA, Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria trial; MARVAL, Microalbuminuria Reduction With Valsartan; RENAAL, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan trial; UA/Cr, uric acid/creatinine ratio.

Another proposed pathway to insulin resistance in obese patients who have diabetes is the ang II-mediated phosphorylation of insulin signaling cascade. Significant vasoconstrictive effects of ang II on pancreatic vasculature hasten islet cell apoptosis. Increased oxidative stress secondary to RAAS activation has also been related to beta cell destruction. RAAS inhibition attenuates this negative response in the islet cells. Furthermore, unaffected bradykinin and NO production from ARBs improves blood flow to the skeletal muscle leading to enhanced insulin-mediated glucose disposal. In part, glucose use is increased by overexpression of GLUT 4.<sup>80,81</sup>

### **Clinical Evidence**

Numerous studies have validated that ARBs, like ACEIs, may also reduce the onset of diabetes in high-risk patients (Table 4). Earlier data from the Antihypertensive Treatment and Lipid Profile in a North of Sweden Efficacy study (ALPINE)<sup>82</sup> showed that candesartan in comparison to hydrochlorothiazide significantly decreased new onset of diabetes (RR = 0.13; CI = 0.02–0.97;  $P = .03$ ). In the CHARM study, candesartan again showed a 19% reduction in the new onset of diabetes (RR = 0.81; CI = 0.66–0.97) compared with placebo in patients who had chronic HF.

Similar results have been reported in the VALUE trial, suggesting a 23% reduction (RR = 0.77; CI = 0.69–0.86;  $P < .001$ ) in new onset of diabetes in a hypertensive population with valsartan in comparison to amlodipine. The CHARM program showed that incidence of developing diabetes showed a 22% reduction in patients receiving candesartan compared with placebo.

In a recent comprehensive meta-analysis, assessment was made pertaining to the onset of diabetes in patients treated with ACEI or ARB.<sup>83</sup> Thirteen randomized trials were included that had enrolled 93,451 high-risk patients who did not have diabetes, of whom 42,780 patients received an ACEI or an ARB. These patients had either hypertension, left ventricular dysfunction, or vascular disease. A total of 2989 new cases of type II diabetes were observed in patients treated with the RAAS-blocking agent (7.12%) compared with 4528 events in 50,671 patients in the control group (8.95%), with an absolute risk reduction of 1.85% ( $P < .001$ ). The number needed to treat to prevent one new case of diabetes averaged 46 over a 4- to 5-year period. Diabetes developed in 6.5% of patients randomized to ACEIs compared with 8.4% in placebo (odds ratio [OR] = 0.73;  $P < .001$ ) and 8.2% in ARBs compared with 10.5% in placebo (OR = 0.73;  $P < .001$ ).

There are multiple limitations in recommending ARBs for prevention of diabetes, however. First, the aforementioned studies had different baseline characteristics. Second, the use of thiazide diuretics and beta-blockers has been variable within all studies, because both agents have deleterious effects on glycemic control. Third, none of the studies have addressed new onset of diabetes as a primary endpoint and most of the data are based on post hoc analyses. Furthermore, the negative results of the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) study have also raised doubts about the role of RAAS blockade for prevention of diabetes.

### **COMBINATION THERAPY WITH ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS IN HIGH-RISK GROUPS**

When we re-evaluate the RAAS, we know that ACEIs block formation of ang II and degradation of bradykinin, whereas ARBs directly inhibit binding of ang II to ATI receptors. As mentioned before, ACEIs may not completely block alternate pathways involved in the formation of ang II. Studies have shown that circulating ang II levels return to normal or may even increase with chronic ACE inhibition. This phenomenon, so-called “ACE escape,” suggests poor long-term inhibition of RAAS with ACEIs. It has been suggested that a more comprehensive RAAS blockade with ACEI and ARB combination may be synergistic because of different sites and mechanisms of action. Recent observations, however, have provided mixed results with combination therapy as an effective option for rendering cardioprotective benefits.

Because of the synergistic effect, combination therapy with an ACE inhibitor and ARB seems more effective than monotherapy for treating hypertension. In a small study of 177 patients who had hypertension, losartan plus enalapril more effectively reduced diastolic blood pressure than either losartan or enalapril alone ( $P = .012$  and  $P = .002$ , respectively).<sup>23</sup>

The Candesartan And Lisinopril Microalbuminuria (CALM)<sup>84</sup> study evaluated the effects of a combination of candesartan and lisinopril on blood pressure and urinary albumin excretion in a high-risk population with microalbuminuria, hypertension, and type 2 diabetes. The combined regimen reduced diastolic blood pressure 16.3 mm Hg compared with 10.4 mm Hg for candesartan and 10.7 mm Hg for lisinopril alone ( $P < .001$ ). The combination therapy reduced the urinary

**Table 4**  
**Angiotensin receptor blocker trials of prevention of type 2 diabetes mellitus by renin-angiotensin-aldosterone inhibition**

Study	Treatment Arm: Subjects who had New DM	Treatment Arm: Subjects who did not have DM	Control Arm: Subjects who had New DM	Control Arm: Subjects who did not have DM	Relative Risk (RR)	CI	P-value Favoring Treatment Arm
LIFE (2002)	241	4006	319	3592	0.75	0.63–0.88	$P = .001$
SOLVD (2003)	9	153	31	138	0.26	0.13–0.53	$P < .001$
ALPINE (2003)	1	196	8	196	0.13	0.02–0.97	$P = .03$
SCOPE (2003)	93	2160	115	2170	0.75	0.62–1.06	NS
CHARM (2003)	163	2715	202	2721	0.81	0.66–0.97	$P < .001$
VALUE (2004)	690	5267	845	5152	0.77	0.69–0.86	$P < .0001$

Abbreviation: NS, not significant; SCOPE, The Study on Cognition and Prognosis in the Elderly; SOLVD, Studies Of Left Ventricular Dysfunction.

albumin/creatinine ratio by 50% compared with 24% for candesartan and 39% for lisinopril alone ( $P < .001$ ). In another study of 108 patients who had progressive chronic renal disease,<sup>85</sup> the combination of valsartan and benazepril significantly reduced systolic and diastolic blood pressures ( $P < .001$ ). This combination also resulted in a  $-0.82 \pm 1.63$  change in the proteinuria/creatinuria ratio from baseline to the end of the study compared with valsartan alone ( $P = .047$ ). The benefits of combination therapy with ACEI and ARB in patients who have HF have been described previously. ValHeFT and CHARM-Added studies clearly showed beneficial effects, with CHARM-Added showing significant reduction in cardiovascular mortality and morbidity in patients who had HF.

### THE ONTARGET STUDY

The Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET)<sup>86</sup> was a landmark trial that evaluated the cardioprotective properties of telmisartan, ramipril, or their combination. This study compared the effectiveness of 80 mg of telmisartan versus 10 mg of ramipril versus combinations of the two in 25,620 high-risk patients. Baseline characteristics included controlled blood pressure, age 55 years or older with a history of CAD, peripheral arterial disease, stroke, or TIA within a week to less than a year, or complicated patients who had diabetes with end-organ damage. Overall, the study population in the ONTARGET was similar to that enrolled in the HOPE trial.<sup>43</sup> The primary outcome was the composite endpoint of cardiovascular mortality, stroke, acute MI, and hospitalization for CHF. Secondary outcomes include newly diagnosed CHF, a revascularization procedure, newly diagnosed diabetes, development of cognitive decline or dementia, new onset of atrial fibrillation, and nephropathy. The study results showed that mean blood pressure was lowered in the telmisartan group (a 0.9/0.6 mm Hg greater reduction than ramipril) and the combination therapy group (a 2.4/1.4 mm Hg greater reduction than ramipril). At a median follow-up of 56 months, the primary events had occurred in 1412 (16.5%), 1423 (16.7%), and 1386 (16.3%) patients, respectively, in the ramipril, telmisartan, and combination groups (RR 1.01 and 0.99 for the telmisartan and combination arms, respectively), showing no difference between the treatment arms. There was no significant difference in other primary or secondary outcomes. None of the secondary outcomes were achieved. When compared with the ramipril group, the telmisartan group had lower rates of cough and angioedema but higher rates

of hypotensive symptoms. In the combination group, there was higher risk for hypotensive symptoms (4.8% versus 1.7%,  $P < .001$ ), syncope (0.3% versus 0.2%,  $P = .03$ ), and renal dysfunction (13.5% versus 10.2%,  $P < .001$ ). This study established the non-inferiority of telmisartan to ramipril. There was no additional benefit of combination therapy because of additive adverse effects (see Fig. 3).

Although in a different group of patients, the results of ONTARGET are in accordance with VALIANT,<sup>59</sup> which compared the effects of dual-agent RAAS blockade in patients who had signs of HF with depressed left ventricular function. Likewise, the non-inferiority of ARB (valsartan) to ACEI (captopril) was confirmed; however, no additional cardiovascular benefit was observed with combined therapy. In ONTARGET and VALIANT, combination therapy was associated with higher rate of side effects and discontinuation rates. Based on these results, there does not seem to be any rationale for the use of combination therapy with ACEIs and ARBs in high-risk hypertensive and post-MI patients. Such a combination is indeed beneficial in patients who have HF, however.

### FUTURE DIRECTIONS

Given the essential contribution of angiotensin II in regulating blood pressure and endothelial function and vascular and cardiac remodeling, RAAS blockade has been inculcated as inevitable part of cardiovascular therapeutics in various conditions. Studies are under way to determine whether doses greater than those used in the previous trials

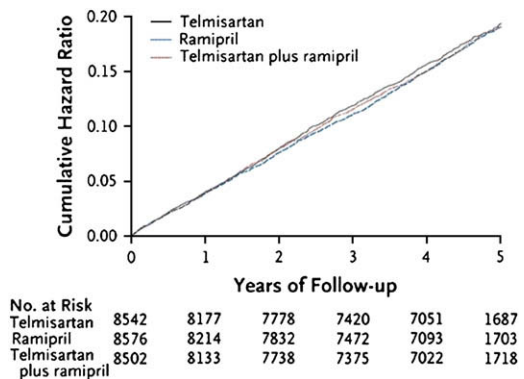


Fig. 3. Kaplan-Meier curves for the primary outcome in the three study groups. The composite primary outcome was death from cardiovascular causes, MI, stroke, or hospitalization for HF. (From ONTARGET Investigators, Yusuf S, Teo KK, Pogue J, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008;358:1553; with permission. Copyright © 2008, Massachusetts Medical Society.)

or combination of ARB and ACEI therapy will provide more extensive RAAS inhibition and greater protection from end-organ damage in various high-risk groups.

The Telmisartan Randomized Assessment Study in ACE-Intolerant Subjects with Cardiovascular Disease (TRANSCEND) trial<sup>87</sup> is evaluating telmisartan in reducing cardiovascular risk independent of blood pressure reduction. The Irbesartan in Heart Failure with Preserved Systolic Function (I-PRESERVE)<sup>88</sup> trial will evaluate irbesartan therapy in elderly patients (>60 years of age) who have a clinical diagnosis of HF with preserved systolic function. The largest secondary stroke prevention trial undertaken to date, Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS),<sup>89</sup> is currently comparing the efficacy and safety of aspirin plus extended-release dipyridamole with clopidogrel, and of telmisartan with placebo, in preventing recurrent strokes. Finally, ROADMAP<sup>90</sup> is a large-scale trial to assess renoprotective effects of olmesartan. This study will assess the onset of microalbuminuria in patients who have type 2 diabetes.

## SUMMARY

When extrapolating results from various clinical studies of the ARBs it should be noted that most ARB trials compared the efficacy of the ARB with another drug. The ValHeft and CHARM studies addressed the specified outcomes comparing the combination therapy with ARBs versus placebo on all-cause mortality or cardiovascular events in HF. None of the trials compared one ARB to another. As a group, these studies do not provide useful information to compare the effectiveness of different ARBs specifically in patients who have high blood pressure and no other compelling indications.

The available level of evidence establishes RAAS blockade as a strategic therapeutic option for high-risk patients because it regulates blood pressure, vascular response to injury, and cardiac and vascular remodeling. Future strategies for treating high-risk patients will focus on early interventions that prevent or delay end-organ damage. The role of ACE inhibitors is well established in this regard; however, there is now substantive evidence that this can be equally achieved with ARBs, which also effectively lower BP and prevent end-organ damage. As our understanding of the pharmacotherapeutics of ARBs improves, the combination RAAS blockade may be reserved for special patient groups, such as those who have diabetic nephropathy or HF. With close consideration of safety and tolerability, individualizing

treatment by using ARBs that have proven efficacy for specific disease states will be the key to this approach.

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