Angiotensin Receptor Blockers: Pharmacology, Efficacy, and Safety

Addison A. Taylor, MD, PhD;[1] Helmy Siragy, MD;[2] Shawna Nesbitt, MD[3]

From the Department of Medicine, Baylor College of Medicine, Houston, TX;[1] the Department of Medicine, University of Virginia, Charlottesville, VA;[2] and the Department of Medicine, University of Texas Southwestern Medical School, Dallas, TX[3]

Key Points and Practical Recommendations

- The angiotensin receptor blockers are highly effective antihypertensive agents that are also particularly well tolerated.
- There are no major differences in efficacy or other clinical characteristics among older drugs in this class, although some of the newer agents may more effectively reduce blood pressure than older agents.
- Major randomized clinical trials have demonstrated that angiotensin receptor blockers provide significant outcomes benefits in conditions such as diabetic nephropathy, chronic heart failure or heart failure following myocardial infarction, hypertension with left ventricular hypertrophy and in patients whose histories of previous events or complicated diabetes puts them at high cardiovascular risk.
- In treating hypertension, angiotensin receptor blockers can be used as first-line therapy or added at later stages of treatment titration.
- These drugs are very effective in combination with thiazide diuretics or calcium channel blockers and there are several single-pill, fixed-dose combinations of angiotensin receptor blockers with hydrochlorothiazide, amlodipine, or aliskiren. These combinations can be given as initial therapy (where appropriate) or later in the course of treatment. Three-drug combinations (angiotensin receptor blocker plus amlodipine plus hydrochlorothiazide and angiotensin receptor blocker plus aliskiren plus hydrochlorothiazide) are also available. *J Clin Hypertens (Greenwich).* 2011;13:677–686.

The renin-angiotensin-aldosterone system (RAAS) plays an important role in protecting vertebrates against cardiovascular collapse due to hypotension and volume loss in the event of traumatic injury that involves blood loss. In certain humans, however, inappropriate or exaggerated activity of the RAAS contributes to the development of hypertension and the initiation of a molecular cascade in tissues with consequent injury to critical organs such as the brain, kidneys, heart, and blood vessels.[1–3] As understanding of the pathologic role of the RAAS in hypertensive vascular disease has unfolded during the past century, so has the interest in developing drugs that could interdict specific components of the RAAS. The first of the RAAS-blocking drugs to become commercially available were the aldosterone antagonists in the 1970s, followed by the angiotensin-converting enzyme (ACE) inhibitors in the 1980s and the angiotensin II receptor blockers (ARBs) in the 1990s. Unlike ACE inhibitors that inhibit the conversion of angiotensin I to II, ARBs bind to the angiotensin II AT_1 receptor, thereby inhibiting the cellular actions of angiotension II mediated by the receptor in which the tissue is located. During the past 20 years, studies in the laboratory and clinic have documented that ARBs, either alone or in combination with drugs of other classes, reduce blood pressure (BP) in hypertensive animals and humans; reduce rates of myocardial infarction (MI), stroke, and progression of renal impairment; and positively impact other markers of cardiovascular (CV) events such as left ventricular hypertrophy (LVH) and urinary protein excretion independent of their effect on BP. Although improvement in mortality and morbidity has been demonstrated after treatment of patients with congestive heart failure (HF) and following MI, this review paper will focus primarily on evidence supporting the use of ARBs in the management of hypertensive patients with and without comorbidities.

Address for correspondence: Addison A. Taylor, MD, PhD, Department of Medicine, Baylor College of Medicine, Houston, TX
E-mail: ataylor@bcm.edu

DOI: 10.1111/j.1751-7176.2011.00518.x

CHEMICAL ENTITIES IN THE ARB CLASS

There are currently 8 drugs commercially available in the United States that share the property of selectively binding to the angiotensin II AT_1 receptor, a receptor that is ubiquitously distributed on most tissues throughout the body. Some of the characteristics of these drugs and their combinations with either thiazide-type diuretics (hydrochlorothiazide [HCT] or chlorthalidone [CLD]) or amlodipine as fixed-dose formulations are summarized in Table I. Not discussed in this review are other drugs that meet the pharmacologic criteria for ARBs but are either still investigational or have never been marketed in the United States because of toxicity.[4]

Pharmacologic Actions Common to All ARBs

All of the drugs in this class bind to the angiotensin II AT_1 receptor thereby inhibiting the multiple actions of

TABLE I. Angiotensin II AT_1 Receptor Blockers Available in the United States

Generic Name	Brand Name	Fixed-Dose Combinations With Thiazide Diuretics	Fixed-Dose Combinations With Other Drugs	Prodrug/Active Metabolite
Losartan	Cozaar	Hyzaar		Losartan/EXP3174
Eprosartan	Teveten	Teveten/HCTZ		
Irbesartan	Avapro	Avalide (irbesartan/HCTZ)		
Valsartan	Diovan	Diovan/HCTZ	Exforge (valsartan/amlodipine)	
			Valturna (valsartan/aliskiren)	
			Valturna/HCTZ (valsartan/aliskiren/HCTZ)	
Telmisartan	Micardis	Micardis/HCTZ	Twynsta (telmisartan/amlodipine)	
Olmesartan	Benicar	Benicar/HCTZ	Azor (olmesartan/amlodipine)	Olmesartan medoxomil/olmesartan
			Tribenzor (olmesartan/amlodipine/HCTZ)	
Candesartan	Atacand	Atacand/HCTZ		Candesartan cilexetil/cardesartan
Azilsartan	Edarbi		(Azilsartan/chlorthalidone)[a]	Azilsartan medoximil/azilsartan
			(Azilsartan/amlodipine)[a]	

[a]Submitted to the Food and Drug Administration for review.

TABLE II. Pharmacologic Characteristics of Angiotensin II AT_1 Receptor Antagonists Commercially Available in the United States[a]

Generic Name	Surmountable (S) or Insurmountable (I) Antagonism	t½, h	Bioavailability, %	Route of Elimination Renal (r) or Biliary (b)	Vd, L	CYP Metabolism
Losartan	S/EXP=I	2/6–9	33	b: 70%; r: 30%	34/12	2C9, 3A4, 1A2
Eprosartan	S	5–7	63	b: 10%; r: 90%	13	No
Irbesartan	I	11–15	60–80	b: 75%; r: 25%	53-93	2C9, 3A4
Valsartan	S	6	23	b: 80%; r: 20%	17	2C9 (weak)
Telmisartan	I	24	43	b: 100%	500	No
Olmesartan	I	14–16	26	b: 60%; r: 40%	17	No
Candesartan	I	9–12	42	b: 40%; r: 60%	10	2C9 (weak)
Azilsartan	S	11	60	b: 55%; r: 42%	16	2C9

Abbreviations: CYP, cytochrome P450; t½, plasma elimination half-life; Vd, volume of distribution. [a]Data obtained from the Food and Drug Administration–approved package insert for each compound.

angiotensin II that are mediated by that receptor, including vasoconstriction, mitogenic activity, cytokine production, reactive oxygen species formation, and aldosterone production. Comparisons of some representative pharmacologic characteristics of the 8 ARBs are included in Table II. There are clearly pharmacologic differences among the various agents. As noted in Table II, certain drugs in the class compete with angiotensin II in a concentration-dependent manner for binding to the AT_1 receptor (surmountable antagonists) while others are insurmountable antagonists that bind irreversibly to the receptor.

It has been proposed that certain pharmacologic effects of ARBs that contribute to their cerebroprotective, renoprotective, and cardioprotective actions documented in clinical trials may be attributable to actions independent of their inhibition of AT_1 receptor activation and subsequent reduction in BP.[5,6] While it is exciting to speculate about the existence of such actions, it has so far been difficult to design a clinical trial that would unequivocally identify an ARB pharmacologic effect in patients with CV disease that is independent of AT_1 receptor blockade and its consequences. In certain experimental models of vascular injury, blockade of the AT_1 receptor by ARBs allows angiotensin II to bind to AT_2 receptors that mediate actions such as vasodilation that counteract those produced by AT_1 receptor activation. The clinical consequences AT_2 receptor activation have not yet been fully elucidated.

Pharmacologic Actions Unique to Specific ARBs

Telmisartan has peroxisome proliferator-activated receptor γ activity at therapeutically achievable doses that may result in a beneficial effect on glucose metabolism in both experimental animal and human models independent of renin angiotensin system (RAS) blockade.[7,8] Super-therapeutic doses of losartan and

irbesartan are required to achieve this same effect. Telmisartan has also been reported to inhibit the proliferation of CV cells.[9]

Both telmisartan and losartan have platelet anti-aggregatory activity that is not shared by valsartan's, candesartan's, or losartan's major metabolite, EXP3174.[10–13]

Losartan also reduces uric acid, an end-product of purine metabolism linked to the progression of renal disease[14] and increased CV risk[15] and implicated in the development of hypertension in children.[16]

It has been hypothesized that these pleiotropic effects of specific ARBs could contribute to the lower incidence of stroke than predicted by BP reduction in outcomes trials of hypertensive patients treated with ARBs compared with treatment with other antihypertensive drugs.[17,18] There was, however, no difference in the incidence of composite fatal and nonfatal CV events or in stroke among patients with high CV risk treated with the ACE inhibitor ramipril or the ARB telmisartan in the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET) study.[19] Stroke rates were not significantly different among other high CV risk hypertensive patients treated with either valsartan or the calcium channel blocker (CCB) amlodipine in the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial, even though systolic/diastolic BP was 2.0/1.6 mm Hg lower in the amlodipine arm than the valsartan arm for the last 68 months of the trial.[20]

The pharmacologic effects of the angiotensin AT_1 receptor antagonists currently available in the United States have been compared in several reviews.[21,22] Differences among these drugs in pharmacologic characteristics such as affinity and type of binding to the AT_1 receptor, plasma half-life of the drug or metabolite, route of elimination, plasma protein binding, bioavailability, and pathway for metabolism are summarized in Table II. The excellent tolerability of all the drugs in this class, whether administered alone or with other drugs that alter their metabolism, provides a wide therapeutic window that allows most of these drugs to be given once daily with 24-hour efficacy in BP reduction.

Pharmacogenomics: Relation to ARB Efficacy

Several splice variants or single nucleotide polymorphisms (SNPs) in the genes of the RAAS have been identified, including those encoding angiotensinogen, ACE, and the angiotensin AT_1 receptor.[23] Correlations with either hypertensive phenotypes and/or with the BP response to drugs that inhibit RAAS components have produced mixed results. Summarized here are only pharmacogenomic studies in hypertensive patients treated with ARBs. In the Swedish Irbesartan Left Ventricular Hypertrophy Investigation vs Atenolol (SILVHIA) trial, 5 different SNPs of the angiotensin AT_1 receptor were identified in 42 patients and correlated with the plasma concentration of irbesartan and BP response to the drug. The plasma concentration of irbesartan was related to the change in systolic BP in individuals homozygous for the AT_1 receptor 5245 T allele, but not for other genotypes.[24] In contrast, there was no association found between ACE insertion/deletion and 12 other polymorphisms of hypertension susceptibility genes and the response of 3503 participants in the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial to either the losartan- or atenolol-based treatment regimens.[25] More analyses are needed of well-characterized gene variants in large patient populations with well-characterized phenotypes to determine whether this is an economically feasible approach to personalizing antihypertensive drug therapy.

Pharmacokinetics

Major pharmacokinetic effects of the 8 ARBs available in the United States are summarized in Table II.[21,22,26,27] All of these drugs are highly protein-bound (>85%) but they vary widely in their volume of distribution from 10 L for candesartan to 500 L for telmisartan. Most of the drugs are dosed once daily, although, based on their short plasma elimination half-lives, losartan and eprosartan may need to be administered twice daily to maintain 24 hours of efficacy in some patients. Bioavailability also varies widely from 23% for valsartan to 60% to 80% for irbesartan. Those drugs that are eliminated primarily via the renal route, such as eprosartan and candesartan, will have higher plasma concentrations in patients with impaired renal function, and lower doses may be needed to achieve the same pharmacodynamic effect as in patients with normal or modestly impaired renal function. Plasma concentrations of both losartan and its active metabolite EXP3174 are decreased when losartan is administered together with rifampin because the latter induces the cytochrome P_{450} isoenzyme 2C9 and accelerates metabolism of both the parent drug and metabolite.[28] Fluconazole, which inhibits 2C9, lowers the concentration of EXP3174 but raises that of the parent drug when coadministered with losartan.[29] The clinical significance of these interactions is unclear.

Adverse Effects: Safety Profile

ARBs are popular with both patients and health care providers in part because of their excellent tolerability. In fact, the adverse effect profiles of the first ARBs to become commercially available were often comparable to or occasionally superior to placebo. Postural dizziness is noted more freqently by patients taking ARBs than those taking placebo, but the incidence of documented postural hypotension is less frequent than this symptom would suggest. The incidence of drug-related cough is comparable to placebo and much less frequent than that which occurs with ACE inhibitors. Similarly, angioedema rates (0.1% to 0.2%) are lower with ARBs than with ACE inhibitors.[30,31] Although

the risk is lower, it has been recommended that ARBs be considered for patients who have experienced ACE inhibitor–related angioedema only if there are no alternatives and the indications are compelling.[32] Hyperkalemia can occur in patients with impaired renal handling of potassium but usually is well tolerated and does not require drug discontinuation. Some increase in serum creatinine is often observed as BP is lowered in patients with modest renal impairment. ARBs, like all other RAS blockers, should not be administered to patients during pregnancy because of the risk of injury or death to the developing fetus.

EFFICACY OF ARBS IN HYPERTENSION

Single-Drug Therapy for Hypertension

All ARBs commercially available in the United States except azilsartan were initially approved by the Food and Drug Administration (FDA) for the treatment of diastolic hypertension. Most studies have demonstrated dose-dependent reduction in BP although the dose response is relatively shallow compared with that of some other antihypertensive drugs such as CCBs. Subsequent studies have demonstrated that drugs in this class are also effective when given as single agents in treating both systolic and diastolic hypertension, isolated systolic hypertension, and hypertensive patients who are elderly or have diabetes and/or the metabolic syndrome. There are reports that ARBs, like ACE inhibitors and possibly all RAS blockers, are less effective in reducing both clinic and ambulatory BP among African Americans than Caucasians, although addition of a thiazide diuretic to the regimen results in equivalent BP reductions in the two ethnic groups.[33]

A recent Cochrane Database Systematic Review evaluated the dose-related trough BP reduction with 9 ARBs, 7 of which are commercially available in the United States, vs placebo in more than 13,000 patients who had been enrolled in 46 randomized controlled trials and followed for 3 to 12 weeks. The average trough reduction in systolic and diastolic BP was −8 and −5 mm Hg, respectively, in a patient cohort whose average pretreatment BP was 156/101 mm Hg.[4] The authors were unable to identify any single drug that was more effective in reducing BP than others. The extent of BP reduction with these 7 ARBs was similar to that produced by ACE inhibitors evaluated under comparable conditions.[34] This observation mirrors the conclusions of a recent report from the Agency for Health Care Research and Quality that compared the relative antihypertensive efficacy of ARBs and ACE inhibitors in 50 studies of patients with essential hypertension and observed no significant difference in these two classes of drugs. The report did note that BP outcomes in trials of longer duration, eg, up to 5 years, were confounded by the coadministration of other antihypertensive drugs in some patients.[35] Since the publication of these reports on the comparative BP-lowering effects of specific ARBs, a new ARB, azilsartan medoxomil (AZL), has been approved by the FDA based on the prespecified primary efficacy criterion of lowering mean 24-hour ambulatory systolic BP rather than the more traditional analysis of seated office trough diastolic BP reduction.[36]

There are relatively few studies that have directly compared specific ARBs in the same patient population. One such study reported that 8 weeks of treatment with the recommended starting dose of olmesartan, 20 mg, produced greater BP reduction than the starting doses of irbesartan (150 mg), losartan (50 mg), or valsartan (80 mg).[37] However, when olmesartan, losartan, and valsartan were compared in a dose-escalation trial of patients with essential hypertension, there was no significant difference in the BP reduction achieved by these 3 ARBs after 12 weeks of treatment.[38] Among 885 type 2 diabetics with overt nephropathy treated for 1 year with either telmisartan 80 mg or valsartan 160 mg daily in the Trial to Investigate the Efficacy of Telmisartan vs Valsartan in Hypertensive Type 2 Diabetic Patients With Overt Nephropathy (VIVALDI) trial, a similar reduction in BP and urinary protein excretion was noted.[39] Attribution of the findings of this trial to ARB alone is confounded by the addition of other antihypertensive medications to control BP. Recently, the FDA approved AZL 80 mg once daily as having superior antihypertensive efficacy (−14.3 mm Hg) to maximum approved daily doses of both olmesartan (40 mg, −11.7 mm Hg) and valsartan (320 mg; −10.0 mm Hg) with no significant difference in adverse event rates. Approval of a superiority claim was based on the results of a pivotal clinical trial comparing the mean change in 24-hour ambulatory systolic BP of the 3 drugs in 1291 patients with stage 1 and 2 hypertension.[36] In a companion study, changes in placebo-subtracted trough seated systolic BP in each of 4 active treatment groups (AZL 20 mg, 40 mg, and 80 mg daily and olmesartan medoxomil 40 mg daily) were similar to the changes in mean ambulatory systolic pressure.[40]

ARBs as Part of Combination Therapy

Fixed-dose single-pill combinations of specific ARBs with other antihypertensive drugs have become widely available in recent years. A number of factors have likely influenced pharmaceutical companies to develop these single-pill combinations. First, it has become more universally accepted that most hypertensive patients will either initially or ultimately require $\geq$2 drugs to achieve BP goals. Low-dose combinations of 2 drugs often produce the same or better BP-lowering effect as higher doses of each component. Certain combinations exhibit fewer adverse effects compared with 1 of the 2 active components. Several studies have repeatedly demonstrated that patients are about 20% more likely to continue taking a 2-drug single-pill combination than they are the same 2 drugs prescribed as separate medications.[41] In the United States, 7 of the 8 commercially available ARBs are also available as single-pill fixed-dose combinations with

the thiazide diuretic hydrochlorothiazide (HCTZ). A combination of the newest ARB, AZL, with the thiazide-like diuretic, chlorthalidone (CLD), is currently under FDA review. In a titration-to-target study of 1085 patients with stage 2 hypertension, AZL/CLD reduced clinic seated trough systolic BP and 24-hour mean systolic BP to a greater extent than olmesartan/HCTZ despite less titration to higher doses[42] in the AZL/CLD group. Several studies have reported fewer adverse effects with the combination than with HCTZ alone, likely because the electrolyte and metabolic disturbances associated with thiazide diuretics are observed less frequently when combined with a RAS blocker. Similarly, the incidence of peripheral edema caused by dihydropyridine CCBs such as amlodipine is significantly reduced when combined with a RAS blocker. There are currently 3 ARB-amlodipine combinations available and a fourth is being developed (Table I). There are currently no outcomes studies with ARB-HCTZ or ARB-CCB combinations. Given the results of the Avoiding Cardiovascular Events through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) trial demonstrating that initial 2-drug therapy for high-risk hypertensive patients with an ACE inhibitor–CCB combination was superior to that of an ACE inhibitor–diuretic combination in reducing CV events,[43] such a trial with an ARB would be of considerable interest. Recently, a fixed-dose combination of valsartan with the direct renin inhibitor aliskiren has been approved for the treatment of hypertension not adequately controlled by other medications, patients not likely to respond to a single BP medication, and patients taking one or the other medications with inadequate BP control.

As was documented in the first Veterans Affairs Cooperative hypertension trial published in 1967,[44] patients with difficult-to-manage hypertension may require $\geq$3 drugs to achieve BP control. Two of the ARBs, valsartan[45] and olmesartan,[46] are now available as part of 3-drug combinations that also include amlodipine and HCTZ. It is noteworthy that combinations that contain all 3 drugs are more effective than a combination that includes any 2 of the 3 drugs. For example, greater mean 24-hour, daytime, and nighttime BP reduction was observed in stage 2 hypertensive patients taking the triple-drug combination of valsartan, amlodipine, and HCTZ than those taking any of the 2-drug component combinations (valsartan-amlodipine, valsartan-HCTZ, and amlodipine-HCTZ).[4-7] In the Triple Therapy With Olmesartan Medoxomil, Amlodipine, and Hydrochlorothiazide in Hypertensive Patients Study (TRINITY), olmesartan combined with both amlodipine and HCTZ resulted in systolic/diastolic BP reductions that were 7.6 mm Hg to 8.4/4.5 mm Hg to 5.4 mm Hg greater than those achieved by amlodipine olmesartan, olmesartan-HCTZ, or amlodipine-HCTZ 2-drug combinations.[46] Yet another single-pill triple-drug combination now commercially available includes valsartan combined with HCTZ and the direct renin inhibitor aliskiren. Patients whose diastolic BP remained >94 mm Hg after 4 weeks of HCTZ 25 mg daily were randomly assigned to one of the following treatment groups for an additional 8 weeks: aliskiren+valsartan+HCTZ, valsartan+HCTZ, aliskiren+HCTZ, or HCTZ alone. Patients receiving valsartan+aliskiren+HCTZ had greater reductions in seated clinic systolic/diastolic BP (−22/−16 mm Hg) and better BP control (67% <140/90 mm Hg) than those treated with either of the 2-drug component combinations,[48] although the adverse event rate was comparable among the 3 groups.[48,49] To date, there have been no clinical trials that have examined the impact of 3-drug combinations, with or without an ARB, on CV outcomes.

SURROGATE MARKERS OF CV OUTCOMES

Proteinuria

Numerous epidemiologic studies[50,51] and at least one outcomes trial[52] have identified a quantitative and continuous association between the amount of albumin in the urine, even in small quantities (microalbuminuria), and the extent of CV risk. Albuminuria also predicts the progression of renal injury toward end-stage renal disease in hypertensive patients and in diabetics regardless of their BP. Although BP reduction is linked to a slowing of the progression of renal disease and to a reduction in albuminuria, particularly in diabetics, ARBs and other RAS blockers have been shown to be more effective in this regard than other classes of antihypertensive drugs.[53] Outcomes studies of hypertensive patients with diabetic nephropathy have documented the superiority of the ARBs losartan and irbesartan vs non-RAS conventional therapy or amlodipine in having fewer patients reach the primary composite end point of doubling of serum creatinine, development of end-stage renal disease, or death, a result that could not be explained by the reduction in BP. Irbesartan therapy was also associated with a reduction in proteinuria in a cohort with similar characteristics. There are few direct comparisons of individual ARBs on proteinuria in patients with diabetic nephropathy. One such trial of 860 patients with type 2 diabetes, urinary protein/creatinine ratio (UACR) of 700, and hypertension found that telmisartan reduced UACR to a greater extent than losartan with no significant differences in BP after 52 weeks of therapy.[54] The authors speculated that this difference might be attributable to pharmacologic characteristics of the 2 drugs since telmisartan has a longer duration of action and is more lipophilic than losartan.

Left Ventricular Hypertrophy

LVH, an independent risk factor for CV events, increases in prevalence with age, obesity, and the extent of BP elevation.[55] Comparisons of changes in

left ventricular mass index has been complicated by differences in measurement techniques and criteria used in various clinical trials. Prevalence of LVH generally correlates with BP level, and therapies that reduce BP cause regression of LVH. Across a spectrum of hypertension intervention trials in which LVH has been measured, RAS blockers, including both ACE inhibitors and ARBs, and CCBs or various combinations of these drugs seem to promote greater reduction in LV mass than do other classes of antihypertensive drugs for the same reduction in BP. This evidence has been summarized in a recent review.[55] However, to identify the drugs that are most effective in reducing LVH, additional trials that directly compare the effects of specific ACE inhibitors, ARBs, and CCBs would be useful.

Development of New-Onset Diabetes

ARBs share with ACE inhibitors the characteristic of having a lower incidence of new-onset diabetes in clinical trials than other classes of antihypertensive drugs.[56,57] There is controversy, however, as to whether treatment with ARBs translates into reduced CV mortality and morbidity compared with other classes of drugs. A post hoc analysis of the VALUE trial indicated that the CV risk of the 1298 hypertensive patients who developed diabetes during the trial was intermediate between the 5250 patients who had diabetes on entry into the trial and the 8697persons who did not develop diabetes during the trial. Although fewer patients randomized to valsartan therapy developed diabetes, those who did had the same CV risk as the new-onset diabetics in the amlodipine treatment group.[58] The results of the ONTARGET trial indicate that treatment of high-risk hypertensive patients with telmisartan had an effect on CV morbidity and mortality equivalent to but not superior to that of the ACE inhibitor ramipril.[59] The CV risk rate in established vs new-onset diabetics vs nondiabetics in this trial has not yet been reported.

Central Aortic Pressure or Arterial Stiffness

It has been reported that ARBs reduce indices of arterial stiffness such as central aortic pressure and pulse wave velocity (PWV) to a greater extent than they do brachial artery cuff pressures in hypertensive patients, perhaps independently of BP reduction.[60,60,61] Although a greater reduction in central than brachial artery pressure observed in the Conduit Artery Function Evaluation (CAFÉ) substudy[62] was provided as an explanation for the greater reduction in CV events among hypertensive patients treated with an amlodipine-based regimen than those treated with an atenolol-based regimen in the Anglo-Scandanavian Cardiac Outcomes Trial (ASCOT),[63] a similar trial comparing an ARB with other agents on both outcomes and estimates of arterial stiffness has not yet been reported.

The combination of an ARB and CCB was more effective in reducing PWV than the same ARB combined with HCTZ, although cuff brachial pressures were reduced to the same extent in a Japanese hypertensive cohort.[64] Both an ARB, valsartan, and an ACE inhibitor, perindopril, reduced central aortic pressure to the same extent in patients with mild hypertension who were previously untreated. The combination of these 2 drugs, however, reduced central aortic pressure more than either drug alone.[65] The clinical implications of these observations have not been investigated to date.

Prevention of Hypertension

The Trial of Preventing Hypertension (TROPHY) was designed to address the hypothesis that interval treatment of prehypertension in young adults would delay or prevent the subsequent development of hypertension. This trial enrolled young adults who met the criteria for prehypertension and treated them with the ARB candesartan vs placebo for 2 years followed by 2 years of placebo. The results demonstrated a reduced frequency with which stage I hypertension occurred in the ARB-treated patients.[66]

Circulating Biochemical Markers of Vascular Inflammation

Angiotensin II has been identified in studies of tissues and experimental animals as a proinflammatory molecule that stimulates the formation of reactive oxygen species, resulting in the upregulation of inflammatory mediators such as the transcription factor NF-κB and increased formation of chemokines, C-reactive protein (CRP), and adhesion molecules and activation of T lymphocytes that contribute to both BP elevation and atherosclerosis.[2,3,67] An increase in circulating markers of inflammation have been documented in patients with hypertension, obesity, and diabetes, and one of these agents, CRP, has been reported to independently predict CV risk.[68] In this context, ARBs along with other RAS blockers should be ideal drugs to block these proinflammatory actions of angiotensin II with a consequent reduction in the levels of circulating markers of inflammation. Studies comparing ARBs with other antihypertensive therapies that have included measurements of high-sensitivity CRP (hs-CRP), tumor necrosis factor α, interleukin 6, monocyte chemotactic protein 1, and the adhesion molecules have, however, yielded inconsistent findings.[69] In several studies, valsartan has reduced hs-CRP compared with either amlodipine or valsartan/HCTZ, whereas it has had no effect on hs-CRP in other studies. Similar heterogeneity of ARB effects on other circulating inflammatory biomarkers suggest that more research is needed before the response of these markers to ARB therapy can be used to reliably and consistently contribute to risk stratification strategies.

Dementia

Both small- and large-vessel infarcts occur more frequently in hypertensive than normotensive individuals. It has been suggested that the subclinical white matter infarcts may contribute to cognitive decline or the

development of dementia among hypertensive patients who have no prior history of clinical cerebrovascular disease.[70] A recent Cochrane Database Systematic Review examined the collective data on cognitive function from 4 outcome trials of hypertensive patients treated with a spectrum of antihypertensive agents or placebo and found no difference among patients taking placebo or active treatment. One of these 4 trials, the Study on Cognition and Prognosis in the Elderly (SCOPE), compared treatment with candesartan vs conventional therapy in elderly patients aged 70 to 89 years on stroke and indices of cognition. Candesartan was slightly more effective at reducing BP than conventional therapy. Although there was a significant reduction in fatal and nonfatal stroke by 23.6% in the candesartan group, there was no significant difference in mini-mental status examination scores in the two groups.[71]

CV/RENAL OUTCOME STUDIES IN HYPERTENSIVE PATIENTS: COMPARISON WITH OTHER DRUGS

The VALUE Trial

This trial was a randomized double-blind multicenter study that involved more than 15,000 hypertensive patients at high risk for cardiac events. The trial was designed to test the hypothesis that for the same BP control, valsartan would reduce cardiac morbidity and mortality more than amlodipine.[20] The main outcome was not different between the two treatments. However, subanalysis revealed that reduction in CV morbidity is related to earlier reduction in BP. Independent of BP control, valsartan compared with amlodipine reduces the risk of developing diabetes mellitus[20,72] and the development of new-onset atrial fibrillation, particularly sustained atrial fibrillation.[73]

The LIFE Study

LVH is an independent CV risk factor. The primary hypothesis of the LIFE study was that losartan would be more effective than atenolol in reducing CV morbidity and mortality in patients with essential hypertension and signs of LVH.[74] For a similar reduction in BP, losartan prevented more CV morbidity and death than atenolol. Echocardiographic results demonstrated greater regression of LVH with losartan than with atenolol.[75] Similarly, losartan lowered the risk of fatal and atherothrombotic stroke more than atenolol.[76] A post hoc analysis also demonstrated a continuous relationship between urinary protein excretion measured as urinary albumin/creatinine ratio, starting at concentrations of microalbumin that were considered below the normal range, and CV events in both diabetics and nondiabetics irrespective of treatment assignment.[52]

The ONTARGET Study

This trial compared ramipril, telmisartan, and the combination of the 2 drugs in patients with vascular disease or high-risk diabetes.[31] The primary composite outcome was death from CV causes, MI, stroke, or hospitalization for HF. BP was lower in both the telmisartan and the combination-therapy groups than in the ramipril group. Telmisartan was equivalent to ramipril in patients with vascular disease or high-risk diabetes. The combination of the 2 drugs was associated with more adverse events without an increase in benefit. Of concern, but unexplained, was the observation that combination therapy reduced proteinuria to a greater extent than either drug alone but was associated with a greater number of patients with renal function deterioration.

The TRANSCEND Trial

The Telmisartan Randomized Assessment Study in ACE-Intolerant Subjects With Cardiovascular Disease (TRANSCEND) trial was a randomized double-blind study comparing telmisartan and placebo in 5926 patients with CV disease or high-risk diabetes who were intolerant to ACE inhibitors and were without HF. The primary outcome was a composite of CV death, MI, stroke, or hospitalization for HF and the secondary outcome was a composite of CV death, MI, and stroke. Telmisartan did not significantly reduce the primary outcome but was associated with a 13% reduction in composite end point of CV death, MI, and stroke.[19]

The RENAAL Trial

The Effects of Losartan on Renal and Cardiovascular Outcomes in Patients With Type 2 Diabetes and Nephropathy (RENAAL) trial was a randomized double-blind study comparing losartan with placebo, both taken in addition to conventional antihypertensive treatment.[77] The primary outcome was the composite of a doubling of the baseline serum creatinine concentration, end-stage renal disease, or death. Secondary end points included a composite of morbidity and mortality from CV causes, proteinuria, and the rate of progression of renal disease. Losartan reduced the incidence of a doubling of the serum creatinine concentration and end-stage renal disease but had no effect on the rate of death. The composite of morbidity and mortality from CV causes was similar in the two groups.

The IDNT

The Irbesartan in Diabetic Nephropathy Trial (IDNT) was a prospective, randomized, double-blind clinical trial that involved 1715 hypertensive patients with nephropathy caused by type 2 diabetes. The trial compared irbesartan, amlodipine, or placebo with regard to the time to the primary composite end point of a doubling of the baseline serum creatinine concentration, the development of end-stage renal disease, or death from any cause.[78] This trial also compared these treatments with regard to the time to a secondary CV composite end point. Treatment with irbesartan was

associated with a lower risk of the primary composite end point doubling of the serum creatinine concentration and development of end-stage renal disease compared with the other two groups. There were no significant differences in the rates of death from any cause or in the CV composite end point.

The IRMA 2 Trial

The Irbesartan Microalbuminuria Type 2 Diabetes Mellitus in Hypertensive Patients (IRMA 2) trial was a randomized double-blind investigation that examined the effect of two different doses of irbesartan, 150 mg and 300 mg daily, on changes in urinary protein excretion in hypertensive, type 2 diabetic patients with microalbuminuria.[79]

The results of the RENAAL[77] and IDNT[78] trials established an important role for losartan and irbesartan, respectively, in the delaying or preventing of decline in renal function in hypertensive diabetic patients who had modest renal impairment at enrollment. Each of these trials reduced the occurrence of the primary end point, a combination of doubling of serum creatinine, development of end-stage renal disease requiring dialysis, or death, compared with conventional therapy that did not include an ACE inhibitor. Parving and colleagues[79] reported that irbesartan reduced the progression of renal dysfunction and reduced urinary protein excretion in hypertensive type 2 diabetic patients, all of whom had microalbuminuria at the onset of the trial.

CONCLUSIONS AND RECOMMENDATIONS

ARBs are attractive agents for both physicians and hypertensive patients because they combine modest BP reduction with excellent tolerability and once-daily administration. They more effectively reduce elevated BP in a broader range of hypertensive patients such as the elderly or African Americans when combined with thiazide diuretics or dihydropyridine CCBs. There are pharmacologic differences among the ARBs, and some drugs in this class have special effects independent of angiotensin II receptor blockade, yet there is currently no strong evidence that these characteristics translate into unique protection against target organ damage from hypertension. Although there are no major differences in the antihypertensive efficacy of maximum doses of older ARBs, newer ARBs may more effectively reduce mean 24-hour systolic BP than maximum doses of older agents in this class. Combinations of ARBs with thiazide diuretics, CCBs, or direct renin inhibitors are very effective. There are several single-pill fixed-dose combinations of ARBs with HCTZ, amlodipine, or aliskiren. These combinations can be given as initial therapy (where appropriate) or later in the course of treatment. Three-drug combinations (ARB plus amlodipine plus HCTZ and ARB plus aliskiren plus HCTZ) are also available. Select ARBs have been documented in clinical trials to reduce CV, cerebrovascular, and renal events among patients following MI and those with impaired renal function, diabetes, and HF. That these outcomes benefits are shared by all members of the class has not been established. Changes in biomarkers of inflammation or tissue injury after ARB therapy have been variable and of limited predictive value in identifying patient subgroups who might derive the greatest benefit from treatment with these drugs. Genetic polymorphisms have also been of limited predictive value in identifying the extent of hypertensive patient response to drugs in this class.

Disclosure: The authors received no honoraria for their contribution to this issue.

References

1. Ferrario CM. Role of angiotensin II in cardiovascular disease therapeutic implications of more than a century of research. *J Renin Angiotensin Aldosterone Syst*. 2006;7:3–14.
2. Harrison DG, Gongora MC. Oxidative stress and hypertension. *Med Clin North Am*. 2009;93:621–635.
3. Savoia C, Schiffrin EL. Vascular inflammation in hypertension and diabetes: molecular mechanisms and therapeutic interventions. *Clin Sci (Lond)*. 2007;112:375–384.
4. Heran BS, Wong MM, Heran IK, Wright JM. Blood pressure lowering efficacy of angiotensin receptor blockers for primary hypertension. *Cochrane Database Syst Rev*. 2008;4:CD003822.
5. Ismail H, Mitchell R, McFarlane SI, Makaryus AN. Pleiotropic effects of inhibitors of the RAAS in the diabetic population: above and beyond blood pressure lowering. *Curr Diab Rep*. 2010;10:32–36.
6. Toth PP. Pleiotropic effects of angiotensin receptor blockers: addressing comorbidities by optimizing hypertension therapy. *J Clin Hypertens (Greenwich)*. 2011;13:42–51.
7. Benson SC, Pershadsingh HA, Ho CI, et al. Identification of telmisartan as a unique angiotensin II receptor antagonist with selective PPARgamma-modulating activity. *Hypertension*. 2004;43:993–1002.
8. Kurtz TW, Pravenec M. Antidiabetic mechanisms of angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists: beyond the renin-angiotensin system. *J Hypertens*. 2004;22:2253–2261.
9. Benson SC, Iguchi R, Ho CI, et al. Inhibition of cardiovascular cell proliferation by angiotensin receptor blockers: are all molecules the same? *J Hypertens*. 2008;26:973–980.
10. Guerra-Cuesta JI, Monton M, Rodriguez-Feo JA, et al. Effect of losartan on human platelet activation. *J Hypertens*. 1999;17:447–452.
11. Jimenez AM, Monton M, Garcia R, et al. Inhibition of platelet activation in stroke-prone spontaneously hypertensive rats: comparison of losartan, candesartan, and valsartan. *J Cardiovasc Pharmacol*. 2001;37:406–412.
12. Sato Y, Fujii S, Imagawa S, et al. Platelet aggregability in patients with hypertension treated with angiotensin II type 1 receptor blockers. *J Atheroscler Thromb*. 2007;14:31–35.
13. Yamada K, Hirayama T, Hasegawa Y. Antiplatelet effect of losartan and telmisartan in patients with ischemic stroke. *J Stroke Cerebrovasc Dis*. 2007;16:225–231.
14. Kang DH, Nakagawa T, Feng L, et al. A role for uric acid in the progression of renal disease. *J Am Soc Nephrol*. 2002;13:2888–2897.
15. Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. *N Engl J Med*. 2008;359:1811–1821.
16. Feig DI, Soletsky B, Johnson RJ. Effect of allopurinol on blood pressure of adolescents with newly diagnosed essential hypertension: a randomized trial. *JAMA*. 2008;300:924–932.
17. Chrysant SG, Chrysant GS. The pleiotropic effects of angiotensin receptor blockers. *J Clin Hypertens (Greenwich)*. 2006;8:261–268.
18. Chrysant SG. Possible pathophysiologic mechanisms supporting the superior stroke protection of angiotensin receptor blockers compared to angiotensin-converting enzyme inhibitors: clinical and experimental evidence. *J Hum Hypertens*. 2005;19:923–931.
19. Yusuf S, Teo K, Anderson C, et al. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. *Lancet*. 2008;372:1174–1183.
20. Julius S, Kjeldsen S, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet*. 2004;363:2022–2031.
21. Oparil S. Newly emerging pharmacologic differences in angiotensin II receptor blockers. *Am J Hypertens*. 2000;13(Pt 2):18S–24S.

22. Norwood D, Branch EI, Smith B, Honeywell M. Olmesartan medoxomil for hypertension: a clinical review, Drug forecast. *P & T*. 2002;27:611–616.
23. Arnett DK, Claas SA, Lynch AI. Has pharmacogenetics brought us closer to 'personalized medicine' for initial drug treatment of hypertension? *Curr Opin Cardiol*. 2009;24:333–339.
24. Kurland L, Hallberg P, Melhus H, et al. The relationship between the plasma concentration of irbesartan and the antihypertensive response is disclosed by an angiotensin II type 1 receptor polymorphism: results from the Swedish Irbesartan Left Ventricular Hypertrophy Investigation vs. Atenolol (SILVHIA) Trial. *Am J Hypertens*. 2008;21:836–839.
25. Nordestgaard BG, Kontula K, Benn M, et al. Effect of ACE insertion/deletion and 12 other polymorphisms on clinical outcomes and response to treatment in the life study. *Pharmacogenet Genomics*. 2010;20(2):77–85.
26. Bramlage P, Schindler C. Differences in pharmacology and their translation into differences in clinical efficacy – a comparison of the renin angiotensin blocking agents irbesartan and losartan. *Expert Opin Pharmacother*. 2010;11(4):521–535.
27. Munger MA. Use of Angiotensin receptor blockers in cardiovascular protection: current evidence and future directions. *P & T*. 2011;36: 22–40.
28. Williamson KM, Patterson JH, McQueen RH, et al. Effects of erythromycin or rifampin on losartan pharmacokinetics in healthy volunteers. *Clin Pharmacol Ther*. 1998;63:316–323.
29. Kaukonen KM, Olkkola KT, Neuvonen PJ. Fluconazole but not itraconazole decreases the metabolism of losartan to E-3174. *Eur J Clin Pharmacol*. 1998;53:445–449.
30. Haymore BR, Yoon J, Mikita CP, et al. Risk of angioedema with angiotensin receptor blockers in patients with prior angioedema associated with angiotensin-converting enzyme inhibitors: a meta-analysis. *Ann Allergy Asthma Immunol*. 2008;101:495–499.
31. 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; 358:1547–1559.
32. Sica DA, Black HR. Current concepts of pharmacotherapy in hypertension: ACE inhibitor-related angioedema: can angiotensin-receptor blockers be safely used? *J Clin Hypertens (Greenwich)*. 2002;4:375–380.
33. Bakris GL, Smith DH, Giles TD, et al. Comparative antihypertensive efficacy of angiotensin receptor blocker-based treatment in African-American and white patients. *J Clin Hypertens (Greenwich)*. 2005;7:587–595.
34. Heran BS, Wong MM, Heran IK, Wright JM. Blood pressure lowering efficacy of angiotensin converting enzyme (ACE) inhibitors for primary hypertension. *Cochrane Database Syst Rev*. 2008;4: CD003823.
35. Matchar DB, McCrory DC, Orlando LA, et al. Comparative Effectiveness of Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin II Receptor Antagonists (ARBs) for Treating Essential Hypertension. Agency for Healthcare Research and Quality, 2007 AHRQ Publication No. 08-EHC003-EF.)
36. White WB, Weber MA, Sica D, et al. Effects of the angiotensin receptor blocker azilsartan medoxomil versus olmesartan and valsartan on ambulatory and clinic blood pressure in patients with stages 1 and 2 hypertension. *Hypertension*. 2011;57:413–420.
37. Oparil S, Williams D, Chrysant SG, et al. Comparative efficacy of olmesartan, losartan, valsartan, and irbesartan in the control of essential hypertension. *J Clin Hypertens (Greenwich)*. 2001;3:283–291, 318.
38. Giles TD, Oparil S, Silfani TN, et al. Comparison of increasing doses of olmesartan medoxomil, losartan potassium, and valsartan in patients with essential hypertension. *J Clin Hypertens (Greenwich)*. 2007;9:187–195.
39. Galle J, Schwedhelm E, Pinnetti S, et al. Antiproteinuric effects of angiotensin receptor blockers: telmisartan versus valsartan in hypertensive patients with type 2 diabetes mellitus and overt nephropathy. *Nephrol Dial Transplant*. 2008;23:3174–3183.
40. Bakris GL, Sica D, Weber M, et al. The comparative effects of azilsartan medoxomil and olmesartan on ambulatory and clinic blood pressure. *J Clin Hypertens (Greenwich)*. 2011;13:81–88.
41. Taylor AA, Shoheiber O. Adherence to antihypertensive therapy with fixed-dose amlodipine besylate/benazepril HCl versus comparable component-based therapy. *Congest Heart Fail*. 2003;9:324–332.
42. Cushman WC, Sica D, Bakris GL, et al. Efficacy and safety of azilsartan medoximil/chlorthalidone vs olmesartan/HCTZ combinations in stage 2 systolic hypertension. *J Clin Hypertens (Greenwich)*. 2011;13(Suppl 1):PO-162.
43. Jamerson KA, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med*. 2008;359:2417–2428.
44. VA Cooperative Study Group. Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. *JAMA*. 1967;202:1028–1034.
45. Calhoun DA, Lacourciere Y, Chiang YT, Glazer RD. Triple antihypertensive therapy with amlodipine, valsartan, and hydrochlorothiazide: a randomized clinical trial. *Hypertension*. 2009;54:32–39.
46. Oparil S, Melino M, Lee J, et al. Triple therapy with olmesartan medoxomil, amlodipine besylate, and hydrochlorothiazide in adult patients with hypertension: the TRINITY multicenter, randomized, double-blind, 12-week, parallel-group study. *Clin Ther*. 2010;32: 1252–1269.
47. Lacourciere Y, Crikelair N, Glazer RD, et al. 24-hour ambulatory blood pressure control with triple-therapy amlodipine, valsartan and hydrochlorothiazide in patients with moderate to severe hypertension. *J Hum Hypertens*. 2011. doi:10.1038/jhh.2010.115.
48. Geiger H, Barranco E, Gorostidi M, et al. Combination therapy with various combinations of aliskiren, valsartan, and hydrochlorothiazide in hypertensive patients not adequately responsive to hydrochlorothiazide alone. *J Clin Hypertens (Greenwich)*. 2009; 11:324–332.
49. Chrysant SG, Murray AV, Hoppe UC, et al. Long-term safety and efficacy of aliskiren and valsartan combination with or without the addition of HCT in patients with hypertension. *Curr Med Res Opin*. 2010;26:2841–2849.
50. Bigazzi R, Bianchi S, Baldari D, Campese VM. Microalbuminuria predicts cardiovascular events and renal insufficiency in patients with essential hypertension. *J Hypertens*. 1998;16:1325–1333.
51. Feldt-Rasmussen B. Microalbuminuria, endothelial dysfunction and cardiovascular risk. *Diabetes Metab*. 2000;26(Suppl 4):64–66.
52. Wachtell K, Ibsen H, Olsen MH, et al. Albuminuria and cardiovascular risk in hypertensive patients with left ventricular hypertrophy: the LIFE study. *Ann Intern Med*. 2003;139:901–906.
53. Kalaitzidis RG, Bakris GL. The current state of RAAS blockade in the treatment of hypertension and proteinuria. *Curr Cardiol Rep*. 2009;11:436–442.
54. Bakris G, Burgess E, Weir M, et al. Telmisartan is more effective than losartan in reducing proteinuria in patients with diabetic nephropathy. *Kidney Int*. 2008;74:364–369.
55. Ruilope LM, Schmieder RE. Left ventricular hypertrophy and clinical outcomes in hypertensive patients. *Am J Hypertens*. 2008; 21:500–508.
56. Elliott WJ, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. *Lancet*. 2007;369:201–207.
57. Abuissa H, Jones PG, Marso SP, O'Keefe JH Jr. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for prevention of type 2 diabetes: a meta-analysis of randomized clinical trials. *J Am Coll Cardiol*. 2005;46:821–826.
58. Aksnes TA, Kjeldsen SE, Rostrup M, et al. Impact of new-onset diabetes mellitus on cardiac outcomes in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial population. *Hypertension*. 2007;50:467–473.
59. Mann JF, Schmieder RE, McQueen M, et al. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. *Lancet*. 2008;372:547–553.
60. Karalliedde J, Smith A, Deangelis L, et al. Valsartan improves arterial stiffness in type 2 diabetes independently of blood pressure lowering. *Hypertension*. 2008;51:1–7.
61. Takami T, Shigemasa M. Efficacy of various antihypertensive agents as evaluated by indices of vascular stiffness in elderly hypertensive patients. *Hypertens Res*. 2003;26:609–614.
62. Williams B, Lacy PS, Thom SM, et al. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. *Circulation*. 2006;113:1213–1225.
63. Dahlof B, Sever PS, Poulter NR, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet*. 2005;366:895–906.
64. Matsui Y, Eguchi K, O'Rourke MF, et al. Differential effects between a calcium channel blocker and a diuretic when used in combination with angiotensin II receptor blocker on central aortic pressure in hypertensive patients. *Hypertension*. 2009;54:716–723.

65. Anan F, Takahashi N, Ooie T, et al. Effects of valsartan and perindopril combination therapy on left ventricular hypertrophy and aortic arterial stiffness in patients with essential hypertension. *Eur J Clin Pharmacol*. 2005;61:353–359.
66. Julius S, Nesbitt SD, Egan BM, et al. Feasibility of treating prehypertension with an angiotensin-receptor blocker. *N Engl J Med*. 2006;354:1685–1697.
67. Lee MY, Griendling KK. Redox signaling, vascular function, and hypertension. *Antioxid Redox Signal*. 2008;10:1045–1059.
68. Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. *Circulation*. 2003;107:391–397.
69. Del FA, Cianchetti S, Celi A, et al. The effect of angiotensin receptor blockers on C-reactive protein and other circulating inflammatory indices in man. *Vasc Health Risk Manag*. 2009;5:233–242.
70. Moorhouse P, Rockwood K. Vascular cognitive impairment: current concepts and clinical developments. *Lancet Neurol*. 2008;7:246–255.
71. Lithell H, Hansson L, Skoog I, et al. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. *J Hypertens*. 2003;21:875–886.
72. Kjeldsen SE, McInnes GT, Mancia G, et al. Progressive effects of valsartan compared with amlodipine in prevention of diabetes according to categories of diabetogenic risk in hypertensive patients: the VALUE trial. *Blood Press*. 2008;17:170–177.
73. Schmieder RE, Kjeldsen SE, Julius S, et al. Reduced incidence of new-onset atrial fibrillation with angiotensin II receptor blockade: the VALUE trial. *J Hypertens*. 2008;26:403–411.
74. Dahlof B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet*. 2002;359:995–1003.
75. Okin PM, Devereux RB, Jern S, et al. Regression of electrocardiographic left ventricular hypertrophy by losartan versus atenolol: the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) Study. *Circulation*. 2003;108:684–690.
76. Kizer JR, Dahlof B, Kjeldsen SE, et al. Stroke reduction in hypertensive adults with cardiac hypertrophy randomized to losartan versus atenolol: the Losartan Intervention For Endpoint reduction in hypertension study. *Hypertension*. 2005;45:46–52.
77. Brenner BM, Cooper ME, De Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*. 2001;345:861–869.
78. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med*. 2001;345:851–860.
79. Parving HH, Lehnert H, Brochner-Mortensen J, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med*. 2001;345:870–878.