Use of Angiotensin Receptor Blockers In Cardiovascular Protection

Current Evidence and Future Directions

Mark A. Munger, PharmD

ABSTRACT

Objective. To differentiate angiotensin II receptor blockers (ARBs) by vascular effects and outcomes in trials on cardioprotective endpoints.

Data Sources. MEDLINE searches were conducted from January 2003 to March 2009 using the following search terms: renin–angiotensin–aldosterone system (RAAS) blockade or inhibition; angiotensin II receptor blocker (ARBs); cardioprotection; vascular protection; end-organ protection; candesartan; eprosartan, irbesartan; losartan; olmesartan; telmisartan; and valsartan. Ongoing and recruiting clinical trials were identified via Clinicaltrials.gov (July 2008).

Study Selection and Data Abstraction. Pertinent basic science research and clinical trials with cardiovascular endpoints and information from reviews, American Heart Association 2009 statistics, and The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines were included in this review.

Data Synthesis. ARBs differ in their vascular protective pleiotropic effects and pharmacokinetic properties, which may contribute to their pharmacological protection to reduce cardiovascular morbidity and mortality, independently of their blood pressure (BP)–lowering effects.

Conclusion. Emerging data show that ARBs are effective in hypertension, left ventricular hypertrophy, postmyocardial infarction, and heart failure. To what extent their pleiotropic effects, independent of BP lowering, contribute to these outcomes will be the focus of research in the coming years. Well-designed, comparative-effectiveness studies are needed to clinically differentiate this class of agents. The future will be marked by multifunctional ARBs that will pharmacologically do more than antagonize the angiotensin type I (AT_1) receptor.

Key words. Atrial fibrillation, candesartan, cardiovascular disease, cardioprotection, end-organ protection, eprosartan, heart failure, hypertension, high blood pressure, irbesartan, losartan, olmesartan, renin–angiotensin–aldosterone system (RAAS), telmisartan, valsartan, vascular protection

INTRODUCTION

Cardiovascular disease (CVD) is a major health problem and a significant economic burden on society. It is the leading cause of death in the U.S., accounting for 1 in every 2.8 deaths.[1] An estimated 80 million American adults have CVD, and 73.6 million of these have hypertension.[2] Significant vascular risk factors for CVD include hypertension, diabetes, dyslipidemia, tobacco use, microalbuminuria, or a calculated glomerular filtration rate (GFR) of between 15 and 60 mL/minute, age, a family history of CVD, physical inactivity, and obesity.[2] These risk factors contribute to a continuum of vascular disease, atherosclerosis, coronary artery disease, and left ventricular hypertrophy (LVH). The result is myocardial infarction (MI) with consequent remodeling of the myocardium, heart failure, and arrhythmias, all contributing to premature death.

The renin–angiotensin–aldosterone system (RAAS), when overexpressed, has long been recognized as a significant contributor to CVD through increases in blood volume and arterial pressure, fibrosis, a prothrombotic state, and progression of vascular lesions. Angiotensin receptor blockers (ARBs), which came into clinical use in the 1990s, are important therapeutic agents for the treatment of CVD. The importance of the pharmacological vascular changes brought about by various ARBs may be an important consideration in the choice of an agent, because although controversial, their effect in BP lowering may be equivalent across the drug class.[3,4]

Randomized trials have established an important role for ARBs at different stages of the continuum of CVD. This article discusses the differences among the ARBs and the current evidence supporting their use in vascular protection.

THE RENIN–ANGIOTENSIN–ALDOSTERONE SYSTEM IN VASCULAR DISEASE

Overexpression of the RAAS leads to a variety of deleterious vascular effects.[5] Direct vasoconstrictive effects occur through cross-talk between angiotensin II among adrenergic, endothelin, and vasopressin pathways, contributing to oxidative stress and reduced nitric oxide activity.[6] Angiotensin II induces endothelial dysfunction via activation of important transcription factors, especially nuclear factor–κβ, thereby inducing proinflammatory phenotypes in vascular smooth muscle. These include:[5]

- activation of NADH and NADPH oxidase, resulting in the production of the superoxide anion

Dr. Munger is Professor of Pharmacotherapy and Internal Medicine and Associate Dean of Academic Affairs at the College of Pharmacy of the University of Utah in Salt Lake City, Utah.

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- activation of monocytes and macrophages
- release of cytokines, proteases, and growth factors
- stimulation of leukocyte adhesion molecules that mediate vessel wall inflammation

Angiotensin II also has a direct effect on smooth-muscle migration, vascular hypertrophy, and the synthesis and release of extracellular matrix composition, all of which contribute to vascular remodeling. A pro-thrombotic state results from the effects of angiotensin II in increasing the synthesis of plasminogen activator inhibitor type 1 (PAI-1) while down-regulating tissue-type plasminogen activator (tPA) and activating platelet aggregation and adhesion.

Finally, angiotensin II receptor overexpression in adipose tissue induces inhibition of peroxisome proliferator–activated receptor-gamma (PPAR)-γ activity, which may lead to insulin resistance. Another proposed mechanism of insulin resistance is angiotensin II–mediated phosphorylation of the insulin-signaling cascade or beta-cell destruction.[7–9]

PHARMACOLOGY AND PLEIOTROPIC EFFECTS

Pharmacology

ARBs do not modulate the amount of circulating angiotensin II; rather, they inhibit the binding of angiotensin II to the angiotensin I receptor (AT_1) (Tables 1 and 2). AT_1 receptors are located primarily in the vascular smooth muscle and adrenal glands.[10] Because they do not have a direct effect on angiotensin-converting enzyme (ACE), ARBs do not directly affect bradykinin; however, they may increase nitric oxide release and inhibit its degradation.[11]

ARBs differ in their AT_1 binding characteristics.[12–14] Binding is classified as surmountable or insurmountable, according to the shifting of the angiotensin II concentration–response curves to the right. Surmountable antagonism does not change the maximal angiotensin II response; insurmountable antagonism reduces the response. Therefore, insurmountable binding cannot be overcome by increasing concentrations of angiotensin II.

Losartan (Cozaar, Merck) and eprosartan (Teveten, Abbott) express surmountable antagonism; the rest of the ARBs have insurmountable characteristics. Of the ARBs, telmisartan (Micardis, Boehringer Ingelheim/Abbott) appears to have the strongest binding affinity to the AT_1 receptor.[15,16] In addition, some ARBs, such as candesartan (Atacand, AstraZeneca), olmesartan (Benicar, Daiichi Sankyo), valsartan (Diovan, Novartis)—but not losartan—can stabilize the AT_1 receptor in an inactive state, called "inverse agonism," in the absence of angiotensin II, thereby attenuating cardiac hypertrophy, independent of BP reduction.[17–19] Some ARBs also block activation of angiotensin II via mechanical stress, supporting the effects of ARBs on AT_1-receptor signaling.[19]

The AT_2 receptor remains enigmatic and controversial, especially in AT_2-coupled interference with pro-inflammatory pathways.[20] It is thought that effects mediated by the AT_2 receptor include inhibition of cell growth, fetal tissue development, modulation of extracellular matrix, neuronal regeneration, apoptosis, cellular differentiation, and, possibly, vasodilation and LVH.[21]

Pleiotropic Effects

ARBs exert salutary effects on vascular biology through their pleiotropic activity. A number of studies have investigated effects of ARBs on endothelial function, oxidative stress and antioxidant properties, platelet function, ventricular re-

Table 1 Pharmacological and Pharmacokinetic Interactions of Angiotensin Receptor Blockers (ARBs)

	Food Interactions	Drug Interactions	Dose in Hepatic Impairment	Dose in Renal Impairment	Cellular Effects*	AT_1-Receptor Binding
Losartan	10% decrease in bioavailability	Rifampin, fluconazole	↓Initial dosage	No change in dose	↓↓URAT1, ↑PPAR-γ, ↓TxA_2/PGH_2	Surmountable
Valsartan	≈50% decrease in AUC (NS)	None	No change in dose	No change in dose	None	Insurmountable
Irbesartan	No	None	No change in dose	No change in dose	↓↓TxA_2/PGH_2, ↑PPAR-γ, ↓cell growth	Insurmountable
Candesartan	No	None	↓Initial dosage in patients with moderate impairment	No change in dose	PPAR-γ	Insurmountable
Telmisartan 80 mg	6%–20% decrease in bioavailability	Digoxin	Use with caution	No change in dose	↑PPAR-γ, ↓↓cell growth, ↓Oxidative stress	Insurmountable
Eprosartan	Delayed absorption (NS)	None	No change in dose	No change in dose (mild-to-moderate renal dysfunction, exercise care in severe disease; no data available)	None	Surmountable
Olmesartan	No	None	No change in dose	No change in dose	None	Insurmountable

AT = angiotensin; AUC = area under the curve; PGH_2 = prostaglandin H_2; PPAR-γ = peroxisome proliferator–activated receptor-γ; NS = not significant; TxA_2 = thromboxane A_2; URAT1 = urate transporter 1.

* PPAR-γ activity occurs at therapeutic dosages only with telmisartan, whereas ↑PPAR-γ activity with other ARBs cannot be achieved with therapeutic dosages.

Table 2 **Pharmacology and Pharmacokinetics of Angiotensin Receptor Blockers**

ARB	Inhibition of Pressor Effect of Angiotensin II	AT_1 Affinity vs. AT_2	Half-life (Hours)	Time to BP Effect (Weeks)	P450 Metabolism	Elimination (Approximate)	F%	T_{max} (Hours)	ABPM 24-hour Mean BP Reduction From Baseline (Systolic BP/Diastolic BP [mm Hg])
Losartan	25–40%	1,000-fold	6–9	3–6	Yes (CYP 2C9 and 3A4)	35% renal 60% hepatobiliary	33	1 (metabolite 3–4)	11–9/7–5
Valsartan	30%	20,000-fold	6	4	Unknown	13% renal 83% hepatobiliary	10–35	2–4	19–8/12–5
Irbesartan	40%	8,500-fold	11–15	2	Yes (CYP 2C9)	20% renal 80% hepatobiliary	60–80	1.5–2	11–10/7–6
Candesartan	TK	10,000	9	2–4	Not significant	33% renal 67% hepatobiliary	15	3–4	13–11/9–8
Telmisartan 80 mg	40%	3,000-fold	24	4	No	<1% renal >97% hepatobiliary	42–58	0.5–1	15–11/11–7
Eprosartan	30%	1,000	20	2–3	No	7% renal 90% hepatobiliary	13	1–2	None
Olmesartan	61%	12,500-fold	13	1–2	No	35%–50% renal 50%–65% hepatobiliary	26	1–3	15–13/11–9

ABPM = 24-hour blood pressure monitoring; ARB = angiotensin receptor blocker; AT_1 = angiotensin type 1 receptor; BP = blood pressure; CYP = cytochrome; F% = bioavailability; T_{max} = time to peak concentration.

Data from Zaman MA, et al. *Nat Rev Drug Discov* 20021:621–636[12] and Barra S, et al. *Exp Opin Pharmacother* 200910:173–189.[13]

modeling, and uric acid concentrations.

Endothelial dysfunction is an important mechanism contributing to the development and progression of CVD. In separate studies in human essential hypertension, irbesartan (Avapro, Bristol-Myers Squibb), telmisartan (but not losartan) promoted endothelium-dependent or endothelium-independent vasodilation, as measured by various modalities of forearm blood flow.[22–24] In type-2 diabetic patients with hypertension, olmesartan decreased serum interleukin-6 (IL-6), and high-sensitivity C-reactive protein (hs-CRP) levels to a greater extent than telmisartan, without differences noted in glycosylated hemoglobin (HbA_{1c}) or adiponectin.[25] Irbesartan reduced inflammatory markers of vascular cell adhesion molecule 1 (VCAM-1), tumor necrosis factor-alpha (TNF-α), and superoxide in normotensive patients with stable coronary artery disease maximally at 12 weeks.[26] Regenerative endothelial progenitor cells (EPCs) were significantly increased by losartan and olmesartan.[26,27] (Angiotensin II accelerates the senescence of EPCs.)

In direct comparison trials, telmisartan (Micardis) reduced the mean reactive hyperemia ratio compared with BP reduction with equivalent doses of valsartan.[28] These improvements in endothelial function may be mediated through expression and distribution of zonula occludens-1 (ZO-1), a protein complex crucial for forming and stabilizing tight junctions between adjacent endothelial cells. Telmisartan, in a dose-dependent manner, increases the permeability of endothelial cells by downregulating ZO-1, versus no effect with valsartan, an effect potentially mediated through an angiotensin II–independent mechanism.[29]

The production of reactive oxygen species (ROS) at levels that significantly exceed the buffering capacity of antioxidant defense systems creates an excess of ROS within the cell, potentially causing damage to vascular cell membranes and leading to cell death. Furthermore, ROS may cause oxidative stress, which has been associated with cardiac hypertrophy and remodeling.

Candesartan, telmisartan, and valsartan can modulate oxidative damage, as measured by a reduction in hydrogen peroxide–induced cell damage in human umbilical vein endothelial cells, and reduce diabetic human urinary 8-epi-prostaglandin-F_2 ($PGF_{2\alpha}$) and 8-hydroxy-2′-deoxyguanosine (OHdG) concentrations, independent of concomitant ACE inhibitor use.[30,31] Both losartan and telmisartan reduced the expression of nitric oxide synthase (NOS) and NADPH oxidase subunit (NOx_1, $p22^{phox}$) genes in a stroke-prone spontaneously hypertensive rat model.[32] Telmisartan reduced expression to a significantly greater degree with the nitric oxide gene, and losartan through the NADPH oxidase gene.

ARBs may alter platelet function by interacting with thromboxane A_2 (TxA_2) in human platelets, thereby reducing TxA_2-dependent platelet activation. Losartan (but not EXP 3174, the losartan active metabolite), irbesartan, telmisartan, and valsartan inhibit healthy human platelet aggregation *ex vitro*.[33] Studies in human hypertension confirm that losartan, but not candesartan, inhibits platelet aggregation, independent of antihypertensive effects.[34] TxA_2 stimulation of human platelets *in vitro* showed that activation was significantly reduced by losartan and irbesartan in a dose-dependent manner; there was an intermediate effect with telmisartan, minimally with maxi-

mal doses of valsartan (5×10^{-6} M) and EXP 3174, but no effect was noted with candesartan.[35] In stroke-prone spontaneously hypertensive rats, *ex vivo* platelet activation expressed by p-selectin, losartan (but not candesartan or valsartan) reduced the number of activated platelets.[36]

Ventricular remodeling and its inherent clinical events have been inconsistently reduced by ARBs.[37–39] In a canine model of localized myocardial injury from transmyocardial direct current shocks, DUP 532, an investigational ARB, failed to prevent increases in left ventricular mass or volume. However, in a post-MI rat model, high-dose losartan improved left ventricular remodeling and reduced fetal gene expression. Valsartan also limited infarct zone remodeling in a myocardial ischemic–reperfusion canine model. Several clinical studies have demonstrated relative equivalency between ACE inhibitors and ARBs in reducing ventricular size in patients with heart failure or following an acute MI.[40,41]

Uric acid levels, a controversial risk factor for CVD, appear to be reduced by ARBs; however, a direct clinical cause-and-effect relationship has not been established. Some ARBs, through a potential probenecid-like effect, modestly reduce uric acid levels with uricosuric effects.[42,43] These effects are related to serum concentrations as well as to intrinsic effects of ARBs on uric acid reabsorption transporters.

PPAR-γ, an intracellular receptor that regulates glucose and lipid metabolism, is modulated by different ARBs. Telmisartan and irbesartan regulate PPAR-γ cofactor binding, thereby exerting selective PPAR modulator activity; however, only telmisartan may exhibit this action at clinically obtainable serum concentrations and independently of AT_1-receptor binding.[43–45]

The spectrum of potential salutary vascular effects exerted by the ARBs has been discussed. Comparative studies of ARBs have shown differences in these pleiotropic effects. A major question is to what extent, if any, do the pleiotropic vascular effects of individual ARBs provide cardiovascular protection?

CLINICAL TRIALS

Several clinical trials have shown the efficacy of ARBs in vascular protection in patients with high-risk hypertension for CVD, left ventricular dysfunction, acute MI, and heart failure (Table 3),[46–49,51,54–58] yet comparative-effectiveness studies of ARBs on vascular outcomes are limited. Although not all of the clinical trials evaluating the efficacy of ARBs were designed to evaluate the cardioprotective effects of these drugs independent of BP control, each trial examined cardiovascular outcomes. BP lowering probably accounts for a significant portion of the ardiovascular benefit observed in these trials.[46]

VALUE. The **V**alsartan **A**ntihypertensive **L**ong-term **U**se **E**valuation (VALUE) trial compared the BP-independent cardioprotective effects of valsartan 80 to 160 mg (Diovan) with amlodipine 5 to 10 mg (Norvasc, Pfizer). Both agents were combined with hydrochlorothiazide (HCTZ), 12.5–25 mg, in 15,245 patients with treated or untreated stage I hypertension who were at high risk for CVD. Patients were observed for a mean of 4.2 months.[47]

At one month of treatment, amlodipine produced a significantly greater reduction in BP compared with valsartan (4.0/2.1 mm Hg vs. 1.5/1.3 mm Hg, respectively; $P < 0.001$). At 72 months, the primary composite endpoint of time to first cardiac event did not differ significantly for patients receiving valsartan (10.6%) and those receiving amlodipine (10.4%). The hazard ratio (HR) was 1.04 (95% confidence interval [CI], 0.94–1.15; $P = 0.49$). The rate of new-onset diabetes was signifi-

Table 3 Trials of Angiotensin Receptor Blockers in Patients With Hypertension and Cardiovascular Disease

Study	Patient Population (No.)	Primary Endpoint (Duration of Follow-up)	Treatments Added to Standard Therapy	Outcome
BPLTTC[49]	HTN and elevated risk of CVD (146,838 patients with 22,666 CV events)	Nonfatal stroke or death from cerebrovascular disease; nonfatal MI or death from CAD, including sudden death; HF causing death or requiring hospitalization	ACE inhibitor or ARB vs. placebo or other drug	• ACE inhibitor RRR = 19% stroke, 16% CHD, 27% HF for each 5-mm Hg reduction • BP-independent CVD protective effects: RRR for CHD = 9% • ARB RRR = 26% stroke, 17% CAD, 12% HF; no BP-independent CVD protective effects
VALIANT[55]	Patients with MI (14,808)	All-cause death	Valsartan alone or in combination with captopril vs. ACE inhibitor	No differences in mortality among groups: 1-year mortality was 12.5% with valsartan, 12.3% with valsartan + captopril, and 13.3% with captopril
UMPIRE[48]	Patients hospitalized for acute coronary syndrome (>65 years) (65,493)	Admission to hospital for acute coronary syndromes (mean, 400 days)	ACE inhibitor vs. ARB as initial therapy	• Adjusted RR = 0.89 (95% CI, 0.76–1.04), not significant • Hospitalization rate: - ACE inhibitor = 15.1 events per 1,000 person-years - ARB = 19.2 events per 1,000 person-years
LIFE[51]	LVH (9193)	Death, MI, or stroke (mean, 4.8 years)	Losartan vs. atenolol	• RRR = 13% (0.021) • CV death = 11% (0.206) • Stroke = 25% (0.001) • MI = –7% (0.491)

table continues

Table 3 **Trials of Angiotensin Receptor Blockers in Patients With Hypertension and Cardiovascular Disease** ***(continued)***

Study	Patient Population (No.)	Primary Endpoint (Duration of Follow-up)	Treatments Added to Standard Therapy	Outcome
VALUE[47]	HTN and high CV risk (male, >50 years, DM, current smoker, high TC, LVH, proteinuria) (15,245)	CV death and CV events (mean 4.2 years)	Valsartan vs. amlodipine	• RRR = not significant • Significantly greater BP reduction with amlodipine (4.0/2.1 mm Hg at 1 month; 1.5/1.3 mm Hg at 1 year; $P < 0.001$ for both comparisons)
CHARM–Alternative[59]	Chronic HF, LVD, ACE inhibitor intolerance	CV death or HF hospitalization (mean 3.7 months)	Candesartan vs. placebo	RRR = 23% (0.0004)
Val–HeFT[57]	Chronic HF (5,010; 366 with no ACE inhibitors)	CV morbidity and mortality (mean 23 months)	Valsartan vs. placebo	Valsartan vs. placebo: mortality + morbidity RRR, 13.2% (RR, 0.87; 97.5% CI, 0.77–0.97)
ONTARGET[61]	High-risk patients with CAD, PAD, or CVD or DM with end-organ damage (25,620)	Composite of CV death, MI, CVA, or HF hospitalization	2 arms: • Telmisartan vs. ramipril • Combination telmisartan + ramipril vs. ramipril	***Telmisartan vs. ramipril*** • RR, 1.01 (95% CI, 0.94–1.09) • Lower rates of cough ($P < 0.001$) and angioedema ($P < 0.01$) and higher rates of hypotensive symptoms ($P < 0.001$); rate of syncope was the same ***Combination therapy vs. ramipril*** • RR, 0.99 (95% CI, 0.92–1.07) • Increased risk of hypotensive symptoms ($P < 0.001$), syncope ($P = 0.03$), and renal dysfunction ($P < 0.001$) • Mean BP reduction was greater with telmisartan (0.9/0/6 mm Hg greater reduction) and combination
OPTIMAAL[54]	High-risk patients with acute MI (5,477)	All-cause mortality Sudden death or resuscitated cardiac death Fatal or non-fatal reinfarction All-cause hospitalization	Losartan vs. captopril	***All-cause mortality*** RRR, 1.13 [95% CI, 0.99–1.28] ***Sudden cardiac death or resuscitated cardiac death*** RRR, 1.19 [95% CI, 0.98–1.43] ***Fatal or nonfatal re-infarction*** RRR, 1.03 [95% CI, 0.89–1.18] ***All-cause hospitalization*** RRR, 1.03 [95% CI, 0.97–1.10]
CHARM–Added[58]	Chronic HF, LVD (2,548)	ACE inhibitor +ARB Composite of CV death or HF Hospitalization (ITT) (mean, 41 months)	Candesartan vs. placebo	RRR, 0.85 [95% CI, 0.75–0.96]
ELITE II[56]	Chronic HF, LVD Stratification by beta-blocker use (3,152)	All-cause mortality Sudden death or resuscitated arrest (mean, 555 days)	Losartan vs. captopril	***All-cause mortality*** HR, 1.13 [95% CI, 0.95–1.35] ***Sudden death or resuscitated death*** HR, 1.25 [95% CI, 0.98–1.60]

ACE = angiotensin-converting enzyme; ACS = acute coronary syndrome; ARB = angiotensin receptor blocker; BP = blood pressure; CAD = coronary artery disease; CHD = coronary heart disease; CI = confidence interval; CV = cardiovascular; CVA = cerebrovascular accident; DM = diabetes mellitus; HF = heart failure; HR = hazard ratio; HTN = hypertension; ITT = intention to treat; LVD = left ventricular dysfunction; LVH = left ventricular hypertrophy; MI = myocardial infarction; PAD = peripheral artery disease; RRR = relative risk reduction; TC = total cholesterol.

Clinical Studies: BPLTCC = Blood Pressure Lowering Treatment Trialists' Collaboration; CHARM = Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity; ELITE II = Evaluation of Losartan in the Elderly Study II; LIFE = Losartan Intervention For Endpoint reduction; ONTARGET = Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial; OPTIMAAL = Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan; VALIANT = Valsartan in Acute Myocardial Infarction; VALUE = Valsartan Antihypertensive Long-term Use Evaluation.

cantly lower with valsartan (13.1%) than with amlodipine (16.4%) (HR, 0.77; 95% CI, 0.69–0.86; $P < 0.0001$).

Cohort Study. A retrospective, propensity-based, cohort study assessed more than 65,000 elderly patients receiving ACE inhibitors or ARBs.[48] Using a 3:1 matching strategy, the investigators compared the rates of hospital admission for acute coronary syndromes (ACS), defined as composite of hospital admission for MI and/or unstable angina, over a period of two years. There were 1,295 hospitalizations for unstable angina. Although the rate of hospitalization for ACS was lower in patients receiving ARBs (15.1 events per 1,000 person-years), compared with ACE inhibitors (19.2 events per 1,000 person-years), this difference did not translate to a significantly lower relative risk (0.89; 95% CI, 0.76–1.04). Subgroup analyses in patients with diabetes, atherosclerosis, or heart failure also did not reveal any differences in CVD outcomes between patients receiving ARBs or ACE inhibitors. CVD outcomes among the various ARBs included in this study were not compared.[48]

BPLTTC. The **B**lood **P**ressure **L**owering **T**reatment **T**rialists' **C**ollaboration meta-analysis of data from 26 trials (17 ACE inhibitors and nine ARBs), comparing ACE inhibitors or ARBs with placebo or another drug class, was conducted to evaluate differences in BP with cardiovascular outcomes in patients with hypertension, diabetes, a history of coronary heart disease, or cerebrovascular disease.[49] For both ACE inhibitors and ARBs, the magnitude of relative risk reduction was correlated with the amount of BP reduction. The odds reduction in the risk of stroke, coronary heart disease (CHD), and heart failure was 26%, 17%, and 12%, respectively, for each 5-mm Hg lowering of BP in patients receiving an ARB. However, analyses did not reveal any BP-independent effects between ACE inhibitors or ARBs on CVD outcomes, although these data might have been limited by the number of patients included.

A direct comparison of three head-to-head trials comparing ACE inhibitors and ARBs demonstrated a 0.7-mm Hg lower mean follow-up systolic BP in patients receiving ARBs, but there was no difference between the two drug types in CVD risk reduction. CIs around the estimates, however, were wide; therefore, a possible effect between the agents cannot be excluded (Figure 1).[49]

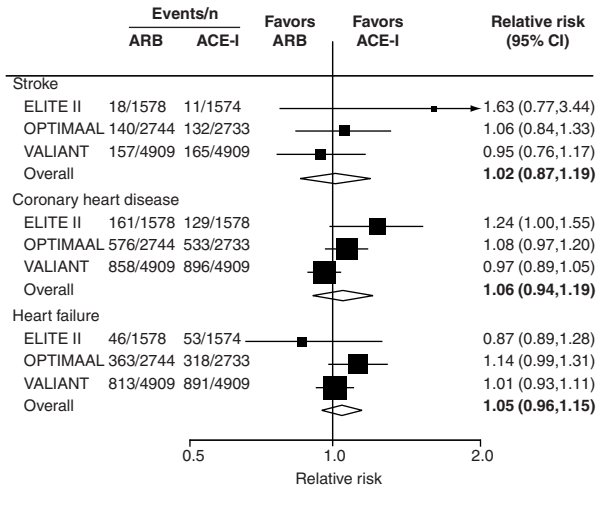


Figure 1 A meta-analysis of 26 large clinical trials comparing angiotensin-converting enzyme inhibitors (ACE-Is) or angiotensin receptor blockers (ARBs) with placebo or other drugs did not reveal significant differences in cardiovascular risk reduction between these agents in outcomes of stroke, coronary heart disease, or heart failure. Diamonds indicate the overall estimate of effect, with width representing the 95% confidence interval (CI), with the center the point estimate of relative risk. (Adapted with permission from Turnbull F, et al. *J Hypertens* 2007;25:951–958. Courtesy of Wolters Kluwer.[49])

Left Ventricular Hypertrophy

LIFE. LVH is an independent predictor of coronary artery disease (CAD), acute cerebrovascular events, and heart failure.[50] The **L**osartan **I**ntervention **F**or **E**ndpoint reduction (LIFE) study was designed to evaluate the BP-independent effects of angiotensin II blockade using losartan for the improvement of LVH and cardiovascular outcomes.[51]

In this double-blind, randomized, parallel-group study, 9,193 patients with hypertension and LVH received losartan (Cozaar) or atenolol (Tenormin) for at least four years. Losartan produced an overall adjusted relative risk reduction of 13%, compared with atenolol for the composite outcome of cardiovascular mortality, stroke, and MI ($P = 0.021$). There was a significant reduction in change from baseline in left ventricular mass index with losartan, compared with atenolol ($P = 0.001$) (Figure 2).[52] Losartan also reduced the incidence of new-onset diabetes by 25%, compared with atenolol ($P = 0.001$).[51]

In an assessment of the relationship between serum uric acid

*$P = 0.21$, adjusted for baseline left ventricular mass index and baseline and in-treatment blood pressure

Figure 2 Data from the *L*osartan *I*ntervention *F*or *E*ndpoint (LIFE) trial revealed that treatment with losartan (Cozaar) resulted in a significantly greater reduction from baseline in the left ventricular mass index compared with atenolol (Tenormin). Echo = echocardiogram. (Adapted with permission from Devereux RB, Dahlöf B, Gerdts E, et al. *Circulation* 2004;110:1456–1462. Courtesy of Wolters Kluwer.[52])

and treatment regimens on the primary composite outcome of the LIFE study, losartan was found to attenuate 29% of the increase in serum uric acid (14%–107%; $P = 0.004$) over 4.8 years of follow-up.[53]

Post-Myocardial Infarction

OPTIMAAL. **Op**timal **T**rial **i**n **M**yocardial Infarction with the **A**ngiotensin II **A**ntagonist **L**osartan (OPTIMAAL) was designed to compare the effectiveness of losartan with captopril (Capoten, Par) in reducing mortality in high-risk patients after an acute MI.[54] Although this study failed to show the superiority or non-inferiority of losartan over captopril for the primary endpoint of all-cause mortality, a nonsignificant difference in all-cause mortality was observed in favor of captopril (18% vs. 16%; respectively; RR, 1.13; $P = 0.07$). Similarly, secondary and tertiary endpoints, including sudden death or resuscitated cardiac arrest and fatal or nonfatal re-infarction, were consistent with primary endpoint findings. However, losartan was better tolerated than captopril, and fewer losartan patients discontinued treatment (17%), compared with those who discontinued captopril therapy (23%) (HR, 0.70; $P < 0.0001$).

VALIANT. A study was conducted to evaluate whether valsartan (Diovan) alone, or in combination with the ACE inhibitor captopril, would result in better survival (all-cause mortality) than captopril alone in patients with acute MI with left ventricular dysfunction, heart failure, or both.[55] In this double-blind study—The **V**alsartan in **A**cute Myocardia**l** **I**nfarctio**n** **T**rial (VALIANT)—patients were randomly assigned to receive valsartan (n = 4,909), valsartan plus captopril (n = 4,885), or captopril (n = 4,909). Patients were followed for a median of 24.7 months.

All-cause mortality rates were similar for valsartan (HR, 1.00; 97.5% CI, 0.89–1.11; $P = 0.98$) and the combination (HR, 0.98; 97.5% CI, 0.89–1.09; $P = 0.73$), compared with captopril alone. The combination of valsartan plus captopril failed to significantly improve CVD outcomes over captopril alone, despite additional lowering of BP, and was associated with a higher number of drug-related adverse events.

Systolic Dysfunction Heart Failure

ELITE II. Intolerance to ACE inhibitors in patients with systolic dysfunction heart failure has prompted the evaluation of ARBs as an alternative therapy. The **E**valuation of **L**osartan **i**n **t**he **E**lderly Study II (ELITE II), a double-blind, randomized, controlled trial of 3,152 patients with symptomatic heart failure, compared effects on mortality, morbidity, safety, and tolerability of losartan (Cozaar) versus captopril (Capoten).[56] This trial did not reveal a significant difference between treatment groups in all-cause mortality (17.7% vs. 15.9%, respectively; HR, 1.13; $P = 0.16$) or sudden death or resuscitated arrests (9% vs. 7.3%; HR, 1.25; $P = 0.08$). Losartan was better tolerated than captopril, and fewer patients discontinued treatment because of adverse events, including cough.

Val–HeFT. When compared with placebo, as in the **Val**sartan **He**art **F**ailure **T**rial (Val–HeFT), valsartan (Diovan) reduced cardiovascular morbidity and mortality 13.2% (RR, 0.87; 97.5% CI, 0.77–0.97) in a study of more than 5,000 patients with New York Heart Association Class II–IV heart failure who remained symptomatic on standard therapy of a diuretic, digoxin, and an ACE inhibitor.[57] There was no difference in mortality between the two groups, but the risk of hospitalization for heart failure was significantly reduced by 27.5% with valsartan.

CHARM–Added. The **C**andesartan in **H**eart failure: **A**ssessment of **R**eduction in **M**ortality and morbidity (CHARM)–Added trial investigated the efficacy of candesartan (Atacand) versus placebo in 2,548 patients already being treated with an ACE inhibitor for chronic heart failure and a reduced left ventricular ejection fraction.[58] Patients were observed for a median of 41 months. The addition of candesartan significantly reduced the primary outcome of cardiovascular death or hospitalization for chronic heart failure compared with placebo (38% vs. 42%; HR, 0.85; $P = 0.011$). Candesartan also reduced the need for multiple admissions for chronic heart failure, suggesting a sustained and durable benefit.

CHARM–Alternative. This trial investigated whether candesartan improved the clinical outcomes of patients with congestive heart failure and left ventricular systolic dysfunction who were intolerant to ACE inhibitors. Candesartan significantly reduced the relative risk of cardiovascular mortality or hospital admission for heart failure by 23% compared with placebo (HR, 0.77; 95% CI, 0.67–0.89; $P = 0.0004$).[59] The clinical benefit was also observed in patients with nonfatal MI, nonfatal stroke, and coronary revascularization. Importantly, hospitalization for worsening heart failure was reduced by 32% ($P < 0.0001$) with candesartan.

Combination Therapies in High-Risk Groups

Does combining an ARB with an ACE inhibitor provide a greater vascular benefit than using either agent alone? Several rationales can be postulated, including increased kinin production and possibly a decrease in aldosterone production, improvements in insulin sensitivity by different mechanisms, and the fact that angiotensin II escape with an ACE inhibitor might lead to AT_2 stimulation during combination therapy. Some clinical trials have provided insight as to whether these rationales can be proven in human vascular disease.

ONTARGET (Telmisartan/Ramipril). A randomized, double-blind study compared the cardioprotective properties of telmisartan (Micardis), ramipril (Altace, King), or their combination in the **On**going **T**elmisartan **A**lone and in combination with **R**amipril **G**lobal **E**ndpoint **T**rial (ONTARGET).[60] The trial enrolled 25,620 patients at high risk of coronary, peripheral, or cerebrovascular disease or diabetes with evidence of end-organ damage. Although the mean BP was lower by –0.9/–0.6 mm Hg in patients receiving telmisartan compared with ramipril, the primary outcome of cardiovascular death, MI, stroke, or hospitalization for chronic heart failure did not differ between treatment groups.[61]

Results showed that telmisartan was non-inferior to ramipril for cardiovascular risk reduction for (1) the primary outcome of death from cardiovascular causes, MI, stroke, or hospitalization for heart failure and (2) the key secondary outcome used in the Heart Outcomes Prevention Evaluation (HOPE) trial[62] of death from cardiovascular causes, MI, or stroke.

Telmisartan was associated with significantly fewer episodes of study discontinuation resulting from cough or angioedema, when compared with ramipril, which was slightly offset by higher rates of hypotensive symptoms but not syncope. Hypo-

tensive symptoms were consistent with lower BP reduction achieved with telmisartan.

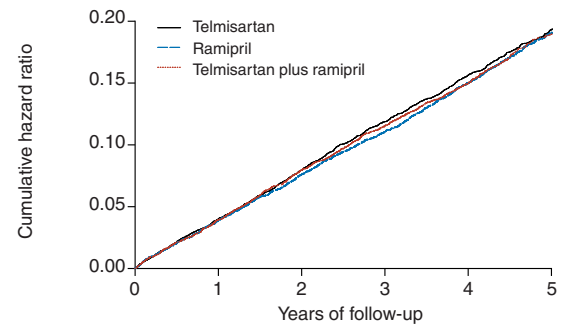
The number of total temporary or permanent discontinuations resulting from adverse effects was significantly lower with telmisartan than with ramipril (RR, 0.94; $P = 0.02$). The telmisartan/ramipril combination resulted in greater BP reductions. However, the combination did not translate into a significant risk reduction over ramipril alone; it was associated with more adverse events (Figure 3),[61] including hypotension, syncope, renal dysfunction, and hyperkalemia.

Other Combination Therapies

Other trials are investigating the effectiveness of ARBs in combination with direct renin inhibitors and calcium-channel blockers.

ALTITUDE (Valturna). In randomized, placebo-controlled trials, the combination of valsartan (Diovan) and aliskiren (Tekturna) provided greater BP reductions compared with either agent alone.[63,64] It is noteworthy that this combination (Valturna, Novartis) maintains a tolerability profile similar to that of either drug alone and of placebo. An ongoing study, **Al**iskiren **T**rial **i**n **T**ype 2 Diabetes **U**sing Cardiovascular and Renal **D**isease **E**ndpoints (ALTITUDE), is evaluating the efficacy of the combination of aliskiren plus an ACE inhibitor or an ARB in reducing cardiovascular morbidity and mortality in more than 8,500 high-risk patients with type-2 diabetes.[65]

EX–FAST (Exforge). A randomized, double-blind, multicenter study, **Ex**forge in **F**ailure **A**fter **S**ingle **T**herapy (EX–FAST), evaluated the efficacy of amlodipine plus valsartan (Exforge, Novartis) in patients with uncontrolled hypertension using monotherapy.[66] BP control was achieved in almost 75% of these patients with the combination.[66]



No. at Risk

Telmisartan	8,542	8,177	7,778	7,420	7,051	1,687
Ramipril	8,576	8,214	7,832	7,472	7,093	1,703
Telmisartan plus ramipril	8,502	8,133	7,738	7,375	7,022	1,718

Figure 3 In the *O*ngoing *T*elmisartan *A*lone and with *R*amipril *G*lobal *E*ndpoint *T*rial (ONTARGET), the Kaplan–Meier curves for the primary outcome of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure were not significantly different between the telmisartan (Micardis), ramipril (Altace), and combination treatment groups. (Reprinted with permission from Yusuf S, et al. *N Engl J Med* 2008;358:1547–1559. Copyright 2008, Massachusetts Medical Society. All rights reserved.[61])

Azor. A study was conducted to evaluate the efficacy and tolerability of olmesartan (Benicar) plus amlodipine (Norvasc) in 1,017 patients with moderate-to-severe hypertension who had been unable to achieve BP control with amlodipine alone.[67] More than 70% of patients achieved BP control with the combination (Azor, Daiichi Sankyo) by 24 weeks.

Twynsta. A randomized, double-blind, placebo-controlled, parallel-group, 4 × 4 factorial trial designed to compare the efficacy and safety of telmisartan (Micardis) plus amlodipine (Norvasc) with both monotherapies in patients with hypertension. After eight weeks, telmisartan 80 mg/amlodipine 10 mg (Twynsta, Boehringer Ingelheim) was associated with significantly lower BP (76.5% overall control; 85.3% diastolic BP control; BP response rates above 90%) compared with both drugs used alone.[68]

ACCOMPLISH (Lotensin and Lotrel). In the randomized, double-blind **A**voiding **C**ardiovascular Events through **Com**bination Therapy in **P**atients **Li**ving with **S**ystolic **H**ypertension (ACCOMPLISH) trial, 11,506 patients with hypertension who were at high risk for cardiovascular events received either benazepril (Lotensin, Novartis) plus amlodipine (Norvasc) or benazepril plus HCTZ. Benazepril/amlodipine (Lotrel, Novartis) was found to be superior to benazepril/HCTZ (Lotensin HCT) in reducing cardiovascular events. The benazepril/amlodipine group experienced an absolute risk reduction of 2.2% and a relative risk reduction of 19.6% (HR, 0.80; 95% CI, 0.72–0.90; $P < 0.001$).[69]

Summary

This question of whether the pleiotropic effects of ARBs with ACE inhibitors would provide a greater vascular benefit than either class of agent alone has not been directly addressed in the clinical trials reviewed here. It is anticipated that translational research techniques will be incorporated into future comparative efficacy trials to determine whether the pleiotropic effects of ARBs are important to the clinical outcomes documented in these studies.

FUTURE DIRECTIONS

The cardiovascular protective benefits of ARBs are still being revealed in numerous trials for indications in addition to hypertension. Ongoing and recruiting trials of ARBs are being conducted to assess the efficacy of ARBs in the following conditions:

- ACS (irbesartan, valsartan)
- myocardial ischemia (valsartan)
- atrial fibrillation (irbesartan, olmesartan, valsartan, telmisartan)
- arterial occlusive disease (olmesartan, candesartan, valsartan)
- stroke (candesartan, telmisartan)
- mitral regurgitation (candesartan)
- hypertrophic cardiomyopathy (candesartan)
- heart failure (irbesartan, valsartan)

Results from these trials will allow better discrimination between ARBs in terms of their efficacy in reducing cardio-

vascular risk in hypertensive patients.

Of particular interest is the potential of ARBs to reduce the risk of atrial fibrillation (AF). the most common arrhythmia. AF is correlated with a significant risk of stroke and thromboembolism.[70,71] The use of ARBs has been associated with a lower incidence of new-onset or recurrent AF. *Post hoc* analyses of the LIFE, VALUE, CHARM, and Val–HeFT trials has revealed a relative risk reduction of 20% to 35% in cases of new-onset AF.[72–75] However, the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico–Atrial Fibrillation (GISSI–AF) study indicated that valsartan did not significantly reduce the time to first recurrence of AF or the proportion of patients who had more than one recurrence of AF over one year in high-risk patients with underlying cardiovascular disease, diabetes, or left atrial enlargement. The findings suggest that more research is needed to define the role of ARBs in the treatment of AF.[76]

In the post-MI setting, ARBs are being investigated in combination with percutaneous coronary intervention (PCI). ARBs differ in their PPAR-γ activity, which may play a role in the prevention of coronary restenosis. An ongoing study is comparing the effectiveness of telmisartan versus valsartan on neointima volume in diabetic patients with an implanted zotarolimus (ABT-578)-eluting stent.[77]

The next generation of ARBs is under investigation, which may enhance facilitation of the vascular mechanisms described earlier in this article. This includes their roles in antagonism at the endothelin receptor, neutral endopeptidase activity, nitric oxide donation, natriuretic peptide elevation, and stimulation of PPAR-γ.[78]

CONCLUSION

There is growing evidence from experimental models of vascular disease and clinical trials that ARBs are an important component in the treatment of cardiovascular disease. Ongoing investigations will add to our knowledge of ARBs compared with other classes of cardiovascular agents, as well as the differences between the ARBs themselves. In the future, we will most likely be learning much more about the many functions of ARBs besides their opposition to the AT_1 receptor.

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