The Comparative Efficacy and Safety of the Angiotensin Receptor Blockers in the Management of Hypertension and Other Cardiovascular Diseases

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Abstract

All national guidelines for the management of hypertension recommend angiotensin receptor blockers (ARBs) as an initial or add-on antihypertensive therapy. The 8 available ARBs have variable clinical efficacy when used for control of hypertension. Additive blood pressure (BP) lowering effects have been demonstrated when ARBs are combined with thiazide diuretics or dihydropyridine calcium channel blockers, augmenting hypertension control. Furthermore, therapeutic use of ARBs goes beyond their antihypertensive effects with evidence-based benefits in heart failure and diabetic renal disease particularly among ACE inhibitor intolerant patients. On the other hand, combining renin-angiotensin system blocking agents, a formerly common practice among medical subspecialists focusing on the management of hypertension, have ceased to do so as there is not only evidence of cardiovascular benefit, but modest evidence of harm, particularly with regard to renal dysfunction. The ARBs are very well tolerated as monotherapy as well as in combination with other anti-hypertensive medications that improve adherence to therapy and have become a mainstay in the treatment of stage 1 and 2 hypertension.

Keywords

Angiotensin Receptor Blockers; Antihypertensive therapy; Clinical Trials; Hypertensio

I. INTRODUCTION

Hypertension is a common disorder in adults around the globe and is among the most common attributable causes of mortality (1). The goal of antihypertensive therapy is to

maintain blood pressures of < 140/90 mmHg for most people (2–7). Recent hypertension guidelines recommend that diuretics, calcium channel blockers (CCBs), angiotensin receptor blockers (ARBs) and ACE inhibitors are all appropriate initial antihypertensive therapies for most people. In the USA, it is suggested that African-Americans with hypertension should be started on diuretics or calcium channels blockers due to evidence-based clinical efficacy results. In addition, the ACE inhibitors or ARBs are advocated for people with stage I–II hypertension and type 1 or 2 diabetes (3).

The ARBs have been in clinical use since 1995 and are known to be effective antihypertensive agent with excellent tolerability profiles. The ARBs have additive BP lowering effects when combined with thiazide diuretics and dihydropyridine calcium channel blockers without increasing adverse event rates. Furthermore, the ARBs have proven mortality and morbidity effects in heart failure and chronic renal disease, particularly when associated with type 2 diabetes. Concerns were raised surrounding the association of ARBs with the development of solid cancers and coronary artery disease. These issues have largely been dismissed by both clinicians and Food and Drug Administration (FDA) regulators (8–10). Herein, we will review the pharmacology and pharmacokinetics of the ARBs. We will also present pertinent research trials comparing the antihypertensive effects and cardiovascular benefits of ARBs including the safety and tolerability issues encountered.

II. PHARMACOLOGY OF THE ARBs

The renin-angiotensin-aldosterone system (RAAS) has been a major target pathway for the development of antihypertensive medications. The four classes of medications that are involved in this pathway include angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), aldosterone antagonists, and direct renin inhibitors. The interest in this pathway is due to the action of angiotensin II on the vascular system, renal sodium and water handling, and cellular proliferation (11). Inhibition of angiotensin converting enzyme only partially inhibits the formation of angiotensin II. Angiotensin II activates two types of angiotensin II receptors (ATR) – ATR_1 and ATR_2. The ATR_1 receptors are abundant in the vessels, brain, heart, kidney, adrenal gland, and nerves while ATR_2 are prominently expressed in the fetus but decrease in number during the postnatal period where they are only available in small amounts in the adult kidney, adrenal gland, heart, brain, uterus, and ovary (12). Activation of ATR_1 increases inositol triphosphate and various arachidonic acid metabolites and decreases cyclic adenosine monophosphate. This causes generalized vasoconstriction from contraction of vascular smooth muscle, increases in aldosterone resulting in increased sodium reabsorption in the proximal tubule and cell growth in the arteries and heart (11). Angiotensin II also facilitates catecholamine release from the adrenal medulla and nerve endings inducing sympathetic nervous system hyperactivity (13). Thus, antagonizing ATR1 causes a reduction in both cardiac afterload and preload (11). The antihypertensive property of ARBs is mainly due to a reduction of peripheral vascular resistance (14). Angiotensin II is believed to have an important mechanistic role in promoting cardiovascular diseases unrelated to its effect in blood pressure. Several animal studies showed that it causes cardiac hypertrophy even in the absence of elevated blood pressure (15). Alderman et al found that individuals with high

renin-sodium profile have greater risk of myocardial infarction than those with a normal or low profile (16).

ATR_2 function remains unclear but its stimulation may inhibit cell growth, cell differentiation, apoptosis and cause vasodilation (17). Animal studies show that AT_2 receptor stimulation improves cardiac function and prevents cardiac remodeling post-myocardial infarction (18).

The 8 ARBs approved for use in the USA and Europe are non-peptide compounds characterized by having biphenyl, tetrazole, benzimidazole, or nonbiphenyl nontetrazole groups (Table 1). Candesartan, olmesartan, irbesartan, losartan, and valsartan have a common tetrazolo-biphenyl structure, candesartan and telmisartan have a common benzimidazole group, and eprosartan has a non-biphenyl, nontetrazole chemical structure (19). With the exception of irbesartan, all active ARBs have a free carboxylic acid group. On the other hand, azilsartan medoxomil is structurally similar to candesartan except it has 5-oxo-1, 2, 4-oxadiazole in place of the tetrazole ring.

The ARBs have more affinity for ATR_1 than ATR_2 and can block the activities of angiotensin II on ATR_1 regardless of whether it was created from angiotensin converting enzyme or other enzymes such as cardiac chymase. ATR_1 binding affinity is not directly correlated with the anti-hypertensive effect of ARBs. All ARBs are insurmountable antagonists except for losartan (14, 20). Higher concentrations of angiotensin II cannot overcome the effect of an insurmountable ARB but the impact of surmountability of AT_1 blockade on final health outcomes has not been established (17).

III. PHARMACOKINETIC CONSIDERATIONS

Table 1 lists the pharmacokinetic characteristics of the 8 available ARBs including half-life, T_{max} (time to maximum plasma concentration), bioavailability, elimination route, drug interaction and cytochrome P450 metabolism (21–29). All ARBs increase renal reabsorption of lithium so concomitant use with lithium should be avoided. Their maximum BP effects occur in about 3–6 hours after administration (14, 19).

Losartan undergoes first pass metabolism in the liver via the cytochrome P450 (CYP) system to form its active metabolite EXP3174, which is 10–40 times more potent than losartan when given intravenously (14). Its dose must be decreased by half in patients with severe hepatic impairment (30). Although food delays its absorption and reduces its peak plasma concentration (Cmax), this is not clinically significant (14). Fluconazole, a CYP2C9 inhibitor, increases the half-life of EXP-3174 but reduces its biological creation from losartan to a greater extent decreasing its area under the curve (AUC) and Cmax by 47% and 30%, respectively. Rifampin, a Uridine 5′-diphospho-glucuronosyltransferase (UDP) glucuronosyl transferase and pan-CYP enzyme inducer, decreases the AUCs of losartan and EXP-3174 by 35% and 40%, respectively. As such, any CYP2C9 enzyme inhibitors or inducers may reduce the effectiveness of losartan and must be considered during drug selection (30).

Three of the ARBs (candesartan cilexetil, olmesartan medoxomil, azilsartan medoxomil) are prodrugs and require activation in the gastrointestinal tract and liver to their active forms (candesartan, olmesartan, and azilsartan, respectively) (31–33). The Cmax of olmesartan is increased among elderly patients by 14% but this is not clinically significant. The mean area under the curve (AUC) for olmesartan is also significantly increased among patients with severe renal impairment (CrCl <20 mL/min) and while caution is advised, dose adjustment is not recommended (32).

Eprosartan, irbesartan, telmisartan, and valsartan are not prodrugs and do not require metabolic activation. Irbesartan has one of the highest bioavailabilities among the ARBs. Irbesartan also exhibits nearly linear dose response with a plateau at 300mg (14, 17, 34). Telmisartan is the longest acting angiotensin II receptor blocker in the market with a mean half-life of 24 hours. It has rapid onset of action of about 0.5 – 1.0 hour (14, 35). Telmisartan co-administration with digoxin increases plasma digoxin level that may lead to toxicity secondary to P-glycoprotein blockade (36). The bioavailability of valsartan is higher in its solution formulation than in capsule form (37).

IV. EFFICACY OF ARBs

A. Blood Pressure Reductions with ARB Monotherapy

Table 2 provides a summary of the initial and maximum doses as well as the dosing intervals for the ARBs (22–29). Antihypertensive efficacy is assessed by determining mean BP reductions from baseline derived from the trough (end-of-dosing period) clinic BP readings or from ambulatory BP measurements. Table 3 lists randomized controlled trials directly assessing inter-agent antihypertensive effectiveness (38–55). The key findings regarding comparative efficacy for ARB monotherapy trials are highlighted below.

In the CLAIM studies, candesartan cilexetil at doses of 16 and 32 mg/day were found to be more potent than losartan at doses of 50 and 100 mg/day, respectively (38–39). Candesartan 16mg/day also reduced clinic BP to a greater extent than losartan 100 mg/day (39). In a trial of olmesartan medoxomil 20 mg/day, ambulatory systolic BPs were lowered more than with valsartan 80 mg/day and losartan 50 mg/day and similarly to irbesartan 150 mg/day (44).

Forced titration of telmisartan from 40 mg and 80 mg/day has been observed to be more efficacious in reducing BP than losartan 50 mg and 100 mg/day (48). In a small study evaluating telmisartan 80 mg/day, less BP reduction was observed compared with valsartan 160 mg/day following 12 weeks of therapy (49). Much larger controlled trials have found that telmisartan 80 mg/day was superior to valsartan 160 mg/day (56). Furthermore, during the last 6 hours of the once daily dosing periods, telmisartan 80 mg/day lowered both systolic and diastolic BP to a greater extent than valsartan 160 mg/day (50).

Irbesartan 300 mg/day but not 150 mg/day has been found to have superior antihypertensive effects to losartan 100 mg/day (51). Irbesartan 150 mg/day did demonstrate greater BP reductions than valsartan 80 mg/day (52). Azilsartan medoxomil 40 mg/day was found to be equivalent to olmesartan 40 mg/day but superior to valsartan 320 mg/day while the antihypertensive effect of azilsartan 80 mg/day was superior to both valsartan 320 mg/day

and olmesartan 40 mg/day using ambulatory systolic BP as the primary efficacy endpoint (53). Eprosartan at 600 and 1200 mg/day significantly reduces BP compared to placebo but has not been studied in comparison with other ARBs (57).

B. Blood pressure Reductions with Combination Therapies

Most hypertension guidelines recommend that combination therapy should be used as initial therapy in stage 2 hypertension or in those patients for whom a single agent does not result in hypertension control. Fixed-dose combination (FDC) pills containing ARBs/diuretics and ARBs/amlodipine are increasingly used in the United States. Diuretic administration leads to activation of the renin-angiotensin system and ARBs blunt this effect allowing for the maximum benefit from diuretic-induced sodium depletion. This complementary action improves tolerability since the dose of the components may be lowered (58). The addition of ARBs also mitigates the negative metabolic effects associated with diuretics including hypokalemia, hyperuricemia, and glucose intolerance (59).

Similarly, the combination of ARBs with amlodipine has been shown to be highly effective and well-tolerated as FDCs. The dihydropyridine calcium antagonists can cause peripheral edema secondary to arterial vasodilatation induced increases in capillary hydrostatic pressure. The ARBs normalize capillary hydrostatic pressure by improving venous return to the heart and hence counteract the effect of amlodipine in a large proportion of individuals with edema. Fogari *et al* showed that amlodipine alone causes increase in ankle-foot volume and pretibial subcutaneous tissue pressure and the addition of an ARB significantly attenuated these effects (60).

Tables 4 and 5 list the randomized controlled trials assessing the efficacy of combination therapies of the ARBs with diuretics and the ARBs with amlodipine versus their component single therapies (61–77). The key findings regarding comparative efficacy for ARB combination therapy trials are highlighted below.

In the 9 trials assessing the impact of adding a thiazide diuretic to an ARB versus the diuretic alone, combination therapy reduced the systolic and diastolic BPs significantly greater than diuretic monotherapy (at equivalent doses) after 6 to 12 weeks (62–69, 77). In one trial the addition of 12.5 mg/day of hydrochlorothiazide (HCTZ) to candesartan 16 mg/day resulted in similar BP reductions as candesartan at 32 mg/day (61).

There are 3 approved ARB/amlodipine FDCs including olmesartan/amlodipine, telmisartan/amlodipine and valsartan/amlodipine. Trials showed that the addition of amlodipine to an ARB resulted in greater BP reductions compared to each component at similar doses. More patients in the combination therapy groups responded to achieve the target BP compared with component monotherapies and with comparable adverse events (72–75). Trials performed in South Korea and Japan have also shown beneficial effects of adding amlodipine to losartan and candesartan but these combinations of losartan/amlodipine and candesartan/amlodipine are not approved in the U.S. (76–77).

Management of hypertension in African-Americans, those with chronic kidney disease, and isolated systolic hypertension in older people are often challenging (78). In ALLHAT, about

31.5% of black men vs 27.2% of non-black men, and 27.2% of black women vs 24.5% of non-black women are taking 3 or more antihypertensive medications (79). These more complicated patient populations have led to the development of FDCs with 3 classes of antihypertensives comprised of a thiazide diuretic, ARB, and dihydropyridine calcium antagonist. The randomized controlled trials assessing the efficacy of these 'triple' FDCs versus their monotherapeutic components are shown in Table 6 (80–81).

Calhoun and colleagues published the first large-scale randomized, controlled trial involving patients with stage I–II hypertension (entry BPs 145/100 mmHg) assessing the efficacy of triple therapy with valsartan, amlodipine and hydrochlorothiazide versus dual therapy with its components. The valsartan/amlodipine/HCTZ combination resulted in mean changes from baseline in BP of 39.7/24.7 mmHg, at maximum doses of each component. The triple therapy was statistically superior to dual therapies (p<0.0001 for triple therapy vs. amlodipine/HCTZ, amlodipine/valsartan, and valsartan/HCTZ). At 8 weeks of therapy, 70.8% of patients in the triple therapy achieved control, 48.3% for valstartan/HCTZ, 54.1% for amlodipine/valsartan, and 44.8% for amlodipine/HCTZ (all p<0.0001) (80).

The TRINITY trial involved 2,492 randomized patients and showed that triple therapy with olmesartan/amlodipine/HCTZ at 40/10/25 mg/day resulted in a 37/22 mmHg reduction in mean BP compared to 27.5/15 mmHg, 30/17 mmHg, 30/18 mmHg blood pressure reductions in amlodipine/HCTZ 10/25mg/day, olmesartan/HCTZ 40/25mg/day, olmesartan/amlodipine 40/10mg/day dual therapies, respectively (all p<0.001). After week 12, 69.9% in the triple therapy achieved goals of BP <140/90 mmHg or <130/80 mmHg for patients with diabetes or chronic kidney disease compared with 41.1%, 53.4%, and 52.9% of the amlodipine/HCTZ, olmesartan/HCTZ, olmesartan/amlodipine combinations, respectively (all p<0.001) (81). This more effective reduction in BP with triple therapy was not affected by race/ethnicity, body weight, or presence of type 2 diabetes mellitus (82–84).

V. USE OF MULTIPLE RENIN-ANGIOTENSIN BLOCKERS

A meta-analysis comprising 38 randomized controlled trials showed no mortality benefit associated with dual ARB and ACE inhibitor therapy and did reveal an increase in non-fatal adverse events including hyperkalemia [potassium level 6.0 mmol/L; RR 1.66 [95% CI, 1.38 to 1.98), p<0.001], hypotension [RR 1.66; (95% CI, 1.38 to 1.98), p<0.001] and increased risk of decline in renal function [creatinine >2.0 mg/dL; RR 1.41 (95% CI 1.09 to 1.84), p=0.01] versus ARB or ACE inhibitor therapy alone (85).

ONTARGET (Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial) showed that although telmisartan/ramipril combination reduced progression of proteinuria in patients with vascular disease [HR 0.76 (95% CI 0.60 to 0.96), p=0.019 combination vs ramipril], the composite primary renal outcome [dialysis, doubling of creatinine, and death; hazard ratio (HR) 1.09, (95% CI 1.01 to 1.18); p=0.037] was actually increased with the combination therapy versus ramipril alone (86).

Similarly, in the ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints) trial, the direct renin inhibitor aliskiren or placebo was added to either a background therapy of ACE inhibitor or ARB was terminated prematurely due to lack of

benefit and increase in hyperkalemia (potassium level 6.0mm/L, 11.2% for aliskerin arm, 7.2% for placebo arm, p<0.001) and reported hypotension (12.1% for aliskerin arm vs. 8.3% placebo arm, p<0.001) (87).

VI. ARBs AND CARDIOVASCULAR OUTCOMES IN PATIENTS WITH HYPERTENSION

Data from the INTERHEART trial (Effect of potentially modifiable risk factors associated with myocardial infarction) showed that hypertension is one of the top risk factors for acute myocardial infarction with an odds ratio of 2.48 (99% CI, 2.30–2.68). Other risk factors identified in this population study included current smoking, raised ApoB/ApoA1, history of diabetes and psychosocial factors (88).

In the LIFE (Losartan Intervention for Endpoint Reduction in Hypertension) trial, losartan was found to reduce cardiovascular morbidity and death by 13% compared to the beta-blocker atenolol (p=0.021) despite similar reductions in BP among hypertensive patients with left ventricular hypertrophy (17). Losartan also reduced the incidence of fatal and nonfatal stroke by 25% compared to atenolol (p=0.002). If contrast, losartan did not reduce cardiovascular mortality or myocardial infarction compared to atenolol (89). In the VALUE (Valsartan Antihypertensive Long-term Use Evaluation) trial, valsartan did not show an advantage over amlodipine in reducing cardiac mortality and morbidity. However, in VALUE there was an unexpected difference in BP control, particularly during the first year of the study with the amlodipine arm resulting in a 17.3/9.9 mmHg versus 15.2/8.2 mmHg in those randomized to valsartan, respectively, p<0.0001). These differences likely contributed to the finding that cardiac events were significantly higher in the valsartan arm (90).

In the SCOPE (Study on Cognition and Prognosis in the Elderly) trial involving 4964 participants aged 70–89 years old with hypertension, candesartan (versus placebo) did not result in significant risk reduction in major cardiovascular event including myocardial infarction and cardiovascular mortality but nonfatal stroke was reduced by 27.8% (95% CI, 1.3 to 47.2, p=0.04) (91).

TRANSCEND (Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease) evaluated high-risk patients intolerant to ACE inhibitors with prior history of cardiovascular disease or diabetes mellitus without heart failure, with about 70% of the participants being hypertensive. Patients were randomized to telmisartan or placebo added to standard of care therapy (excluding a renin-angiotensin blocking therapy). After 56 months of follow-up, telmisartan resulted to fewer major cardiovascular events compared with placebo (15.7% versus 17.0%, respectively) but the result was not statistically significant [HR 0.92 (95% CI, 0.81 to1.05), p=0.216] (92).

VII. ANGIOTENSIN RECEPTOR BLOCKERS IN DIABETES AND KIDNEY DISEASE

The ARBs have been used to reduce intraglomerular hypertension in patients with diabetic nephropathy. By reducing the gradient within the glomerulus, the hypothesis is that fibrosis

of the nephron will be averted. The IRMA 2 (Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria) trial showed that over 1 year in patients with hypertension, type 2 diabetes mellitus and microalbuminuria, fewer participants progressed to macroalbuminuria in patients treated with irbesartan compared to placebo with hazard ratios (HR) of 0.30 in the irbesartan 300 mg/day (95% CI, 0.14 to 0.61; P< 0.001) and 0.61 in the irbesartan 150 mg/day (95% CI, 0.34 to 1.08; p=0.08) (93).

The MARVAL trial (Microalbuminuria Reduction With Valsartan in Patients With Type 2 Diabetes Mellitus) compared the anti-proteinuric effects of valsartan and amlodipine in patients with type 2 diabetes and microalbuminuria. Both arms targeted a blood pressure of 135/85 mmHg. The urine albumin excretion rate at 24 weeks with valsartan 80 mg/day was 56% of baseline compared to 92% of baseline with amlodipine 5 mg/day (p<0.001). Additionally, more patients reversed to normoalbuminuria with valsartan compared with amlodipine (29.9% versus 14.5%, respectively; p<0.001) (94).

The RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) trial included patients with Type 2 diabetes mellitus with nephropathy. Losartan reduced the incidence of doubling of serum creatinine (risk reduction, 25%; p=0.006) with 35% reduction in proteinuria and reduced incidence of end-stage renal disease (risk reduction 28%; p=0.002) versus placebo but without mortality benefit. Except for lowering the rate of first hospitalization from heart failure (risk reduction of 32%; p=0.005), the composite of morbidity and mortality from cardiovascular causes was similar between losartan therapy and placebo after 3.4 years of therapy (95).

In the IDNT (Irbesartan Diabetic Nephropathy Trial) involving hypertensive patients with diabetic nephropathy, the irbesartan arm had a 37% lower risk of doubling the serum creatinine versus the amlodipine arm (p<0.001) and 33% lower than the placebo group (p=0.003). Development of end stage renal disease was nominally lower with irbesartan use compared with amlodipine use and placebo but it did not reach statistical significance (p=0.07) (96).

VIII. ANGIOTENSIN RECEPTOR BLOCKERS IN POST-MYOCARDIAL INFARCTION AND HEART FAILURE

Angiotensin blockade is a major therapeutic strategy in patients with heart failure by providing a balanced reduction in preload and afterload when reduced systolic function occurs post-ischemic event or due to non-ischemic cardiomyopathy. The ARBs have been compared in a number of trials to the ACE inhibitors in patients with systolic heart failure. In ELITE II (Losartan Heart Failure Survival Study), losartan 50 mg/day was not found to be superior to captopril 150 mg/day (given in 3 doses) in reducing all-cause mortality in heart failure patients with NYHA classes II–IV and an LVEF 40%. Of note, approximately 80% of the patients in ELITE II had ischemic causes of heart failure and 50% were classified as NYHA class II (mild-moderate). There was an average annual mortality of 11.7% in the losartan arm versus 10.4% in the captopril arm [HR 1.13, (95% CI, 0.95 to 1.35), p= 0.16]. In addition, 142 and 115 sudden deaths or resuscitated cardiac arrests were recorded in the losartan and captopril groups, respectively [HR 1.24, (95% CI 0.97–1.59),

p=0.08]. Not surprisingly, fewer patients discontinued treatment prematurely in the losartan group compared to captopril due to adverse effects (9.7% compared with 14.7% respectively, p=0.001) (97).

The VALIANT (Valsartan in Acute Myocardial Infarction) Study showed that valsartan was as effective as captopril in reducing all-cause mortality among patients with history of acute myocardial infarction [valsartan group versus captopril, HR 1.00 (97.5% CI, 0.90 to 1.11); p=0.98] but the combination of captopril plus valsartan did not prove to be superior to the monotherapy regimens (98). The OPTIMAAL (Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan) Study demonstrated that another ARB, losartan, was comparable to captopril in reducing overall mortality in patients with history of myocardial infarction and heart failure with left ventricular dysfunction (LVEF <35%) [RR 1.13 (95% CI, 0.99 to 1.28), p=0.07] (99).

The CHARM (Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity) study was actually composed of 3 trials – CHARM Alternative (LVEF 40% and ACE intolerant) versus placebo, CHARM Added (LVEF 40% to patients already on ACE inhibitors) and CHARM Preserved (LVEF > 40%) and are also placebo controlled (100). In the CHARM Alternative study, candesartan was associated with significant 23% relative risk reduction in CV death or hospitalization for CHF with a number needed to treat of about 14 patients (101). In CHARM Added, candesartan was associated with a significant 15% relative risk reduction of CV death or hospital admission with absolute risk reduction of about 4% after 41 months of median follow-up. There was higher permanent discontinuation rate in the candesartan group compared with placebo group (24% versus 18%, p=0.0003) due to adverse events including hyperkalemia and doubling of serum creatinine. (102). In CHARM Preserved trial, there was no significant reduction in cardiovascular mortality and morbidity in patients with preserved left ventricular function receiving candesartan versus placebo after 36.6 months of follow-up (103).

Val-HeFT (Valsartan Heart Failure Trial), demonstrated beneficial effects of ARBs in heart failure patients, particularly through those participants unable to tolerate ACE inhibitors. Patients with chronic heart failure with New York Heart Association (NYHA) functional classes of II–IV were randomized to receive valsartan (target dose of 160 mg twice a day) or placebo. The valsartan group had fewer combined end point of mortality and morbidity defined by cardiac arrest with resuscitation, hospitalization for heart failure, or administration of intravenous inotropic or vasodilator drugs [RR 0.87 (97.5% CI, 0.77 to 0.97); p=0.009]. There was also significant improvement in NYHA class, ejection fraction, and quality of life in the valsartan arm compared to placebo (p<0.01). In contrast to CHARM-added (102), the addition of valsartan to an ACE-inhibitor adversely affected mortality (p=0.009) and had a trend toward increases in combined mortality and morbidity (p=0.10) (104).

To date, there is no established specific therapy for heart failure associated with preserved ejection fraction (HFpEF) other than maintaining good BP control and managing volume status. As noted above in the CHARM-Preserved trial, there was no improvement in the primary outcome for candesartan relative to placebo (103). A second and larger trial - I-

PRESERVE - involved patients at least 60 years of age with NYHA class II–IV and LVEF of at least 45%. Irbesartan 300mg/day did not reduce mortality or hospitalization for any cardiovascular cause compared to the control group. Rates of hospitalization due to cardiovascular causes were 70.6 and 74.3 per 1000 patient-years in the irbesartan and placebo groups, respectively [HR 0.95 (95% CI, 0.85 to 1.08), p=0.44] (105).

IX. SAFETY AND TOLERABILITY OF ARBs IN HYPERTENSION

A. Safety of the ARB Monotherapies

The ARBs have demonstrated excellent safety profiles alone and in combination with other antihypertensive therapies during the past 20 years. The tolerability profiles of ARBs are similar to placebo and superior to the ACE inhibitors. For example, the ACE inhibitors increase the risk of cough two- to three-fold over placebo and may cause up to 0.1% – 0.2% rates of angioedema which can be life threatening in a minority of the cases (106). Cough and angioedema most likely result from the accumulation of bradykinin and substance P, which are both degraded by ACE, and they recur with the reintroduction of the ACE inhibitor or use of another ACE inhibitor (107). In a meta-analysis involving 11 randomized controlled trials comparing the tolerability of ARBs versus ACE inhibitors, diuretics and placebo, the cough risk of the ARBs was comparable to placebo [RR 1.01 (95% CI, 0.74 to 1.39) (108). Among patients intolerant to ACE inhibitors, angioedema was a rare event among ARB users with an incidence of 0.12% versus 0.07% in the placebo arm [RR 1.62 (95% CI, 0.17 to 15.79)]. Compared to placebo, ARB use was associated with higher risk of renal dysfunction, hypotension and hyperkalemia (107). Despite these findings, discontinuation events were similar in patients treated with ARBs, diuretics [RR 1.50 (95% CI, 0.26 to 8.52)], or placebo [RR 0.99 (95%CI, 0.84 to 1.17)] (108). Hence, the ARBs have been demonstrated to be one of the better tolerated antihypertensive class with improved persistence in the management of hypertension or other co-morbidities and the class that is an appropriate option for patients who are intolerant to ACE inhibitors.

The most commonly reported adverse events in randomized controlled trials comparing angiotensin receptor blockers to placebo include headache, respiratory infection, dizziness, and fatigue. In these analyses, the rates of adverse events on ARBs were comparable to that of placebo. Reported discontinuation rates in major ARB trials are low. For example, Anderson and colleagues reported just 1.5% patients withdrew from their clinical study due to adverse events (38). In a study comparing losartan and candesartan performed by Bakris et al, 4 of the 654 patients (0.6%) on either candesartan or losartan required hospitalization but none was considered treatment-related. Withdrawal from the study was rare and comparable between treatment arms (55). Oparil et al reported 7 out of 588 (1.2%) patients discontinuing from her study evaluating comparative efficacy and safety of olmesartan, valsartan, and irbesartan due to adverse events including fatigue, malaise and cough (44). In a similar trial, Giles et al reported 16.9%, 13.5%, 10.3% and 17.9% total discontinuations for olmesartan, losartan, valsartan and placebo, respectively. Less than 1% of the randomized patients reported serious adverse events and all were considered unrelated to the medication (45).

In 2012, a gastroenterology group at the Mayo Clinic published a case series involving 22 patients suggesting an association of olmesartan medoxomil with the development of sprue-like enteropathy based on clinical presentation, histopathology and temporal relationship to the drug (109). In July 2013, FDA issued a warning that olmesartan may cause sprue-like enteropathy but this warning was later removed from the label of the drug (110). A case control study published recently (111) showed no statistically significant association between olmesartan and diarrhea among patients undergoing upper endoscopy (OR 1.99; 95% CI, 0.79–5.00) and colonoscopy (OR 0.63; 95% CI 0.23–1.74).

In a trial that compared the efficacy and safety of telmisartan, valsartan and placebo, seven patients out of 207 withdrew from the study due to adverse events. Treatment related adverse events were reported as 2.1% on telmisartan 40mg, 4.5% on telmisartan 80mg, 2.8% on valsartan 80mg and 3.5% on valsartan 160mg (47).

Discontinuation rate for irbesartan 300mg (1.4%) have been reported to be comparable to placebo (3.4%), and the lower dose of irbesartan (150mg) (2.1%). Again, like other ARBs described above, the overall reported adverse events including headache, musculoskeletal pain, dizziness and fatigue were comparable between irbesartan and placebo (51). No serious adverse events have been considered due to irbesartan (0.5%) or valsartan (1.4%) use (52).

B. Safety of ARBs in Combination with Thiazide Diuretics

A number of large safety and efficacy randomized controlled trials of ARB/thiazide diuretic combination therapies have reported adverse events that were mild to moderate in intensity, transient and generally unrelated to the study drug. The safety and tolerability of the different ARB-diuretic combinations are similar to each other.

Candesartan-hydrochlorothiazide—Reported adverse events on trials with ARB in combination with thiazide diuretics (HCTZ) are mild to moderate, transient and/or unrelated to treatment. Evaluation of the safety of candesartan/HCTZ 16/12.5 mg/day have not shown serious adverse events and other than one case of hypokalemia with the combination therapy none were considered treatment-related (61). In a 24-week study of the lower doses of this combination (candesartan/HCTZ 8/6.25 mg/day), there were no significant changes in plasma glucose, hemoglobin A1c, LDL, HDL creatinine, potassium and uric acid. No serious adverse events and discontinuations due to adverse events were reported (112). Higher doses of fixed-dose combination with candesartan/HCTZ 32/12.5 mg/day or 32/25 mg/day has also found to be safe and well tolerated. In a large pooled analysis of safety, Mengden et al reported 49 out of 4098 patients (1.2%) having adverse events, 7 of which were considered serious (0.2%) (113).

Eprosartan-HCTZ—The ARB eprosartan was studied by Sachse et al who reported 65 out of 157 (41.4%) patients having an adverse event of which 19 were probably treatment-related in the eprosartan monotherapy group (600 mg/day) compared to 69 out of 152 (45.4%) patients of which 25 were probably treatment related in the eprosartan/HCTZ combination group (600/12.5 mg/day) (62).

Olmesartan-HCTZ—In a trial involving olmesartan/HCTZ combinations of 40/25 mg/day, 20/25 mg/day, 40/12.5 mg/day, and 20/12.5mg/day, no differences in adverse events by treatment group thought to be related to drug were reported. About 0.19% patients had serious adverse events and none were reported due to study drug (63). Fogari et al reported 3.9% of patients in an olmesartan/HCTZ 40/12.5 mg/day group had drug related adverse events compared to 0.7% in the olmesartan 40 mg/day monotherapy treatment arm. About 2.3% patients and 1.4% patients discontinued from the study due to adverse events in the combination group and monotherapy group, respectively (114).

Losartan-HCTZ—The percentages of adverse events, both laboratory and clinical, in the trials of losartan/HCTZ combination therapy at different doses were comparable to placebo except for the incidence of dizziness, which was more common in the combination group with (64). The combination therapy with losartan/HCTZ 100/25 mg/day had fewer total clinical adverse events than losartan monotherapy 150 mg/day (43.3% versus 52.6%) including a rise in creatinine (0.5% versus 1.1%). Reported serious adverse events were also greater with monotherapy compared with combination therapy (3.6% versus 1.0%, respectively) but these findings were not statistically significant (65).

Irbesartan-HCTZ—Th*e* INCLUSIVE TRIAL (66) had 3% serious adverse events with 3 occurring in the placebo arm, 4 in the HCTZ monotherapy 12.5 mg/day, 8 in the irbesartan/HCTZ 150/12.5 mg/day, and 7 in the irbesartan/HCTZ 200/25 mg/day. All were judged as unrelated to the medication except for one event of hypotension in the irbesartan/HCTZ 150/12.5 mg/day which was probably drug related (66). Lapuerta et al (115) actually reported more adverse events with irbesartan monotherapy than irbesartan/HCTZ combination therapy 300/25 mg/day (36.1% versus 29.9%). However, hyperkalemia and hypokalemia was slightly more common with the combination therapy (0.2% and 0.6%, respectively) than with monotherapy (0% and 0.4%, respectively). Hypotension and dizziness were rare in both treatment arms. Severe hypokalemia (< 3 mmol/L) was not observed (115).

Valsartan-HCTZ—With forced-titration, dizziness was more frequent in the combination of valsartan/HCTZ therapy than with monotherapy (160/320+12.5/25mg) (67). Otherwise, the safety profile of valsartan/HCTZ combination therapy was comparable to valsartan monotherapy. Discontinuation rates were greatest with valsartan monotherapy 320 mg/day (7.1%) compared to 3.0% in the valsartan/HCTZ combination and 2.4% in the placebo group. During the 54 week extension of the study, treatment related adverse events were identified in 14.9% of patients receiving valsartan/HCTZ 320/25 mg/day and 10.5% of patients on valsartan/HCTZ 320/12.5 mg/day (116). In a meta-analysis done by Weir et al, there was increasing frequency of reported dizziness at increasing component doses of valsartan/HCTZ therapy (117). Finally, hyperuricemia was reported less often with valsartan/HCTZ than with HCTZ alone (5.0% versus 8.6% respectively) (118).

Telmisartan-HCTZ—Lacourciere and coworkers have reported that telmisartan/HCTZ combination therapy had a similar discontinuation rate compared to telmisartan monotherapy. The incidence of adverse events between these two therapies were also

comparable. Although more patients in the combination group complained of dizziness, this finding did not reach statistical significance (68). Neldam et al reported comparable drug related adverse events between telmisartan/HCTZ 80/25 mg/day and 80/12.5 mg/day (5.7% versus 5.0%, respectively) resulting in discontinuation percentages of 1.7% and 3.0%, respectively. Two of the serious adverse events were reported as drug-related including atrial flutter in a patient receiving 80/25 mg/day of the combination medication and third degree atrioventricular block in another patient on 80/12.5 mg/day of the combination medication. Hypokalemia was rare (70).

Azilsartan-chlorthalidone—In a pivotal study of this newer ARB with the diuretic chlorthalidone, Sica *et al* reported higher rates of increases in creatinine and dizziness in the higher doses of azilsartan/chlorthalidone combination than with chlorthalidone alone. Hypotension was rare but there were 3 reported episodes of syncope in the combination group. The reported cases of rise in creatinine were transient and values returned to baseline after drug discontinuation (71).

C. Safety of ARBS in Combination with Amlodipine

A number of large safety and efficacy randomized controlled trials of ARB/amlodipine combination therapies report adverse events that were low and mild to moderate in intensity, transient and typically unrelated to the study drug. The safety and tolerability of the different ARB-amlodipine combinations are similar to each other.

Olmesartan-amlodipine—Chrysant *et al* reported comparable treatment related adverse events between the combination of olmesartan/amlodipine and placebo (19.6 to 33.1% versus 29.6%, respectively). The frequency of peripheral edema was lower in patients treated with olmesartan/amlodipine in combination compared to amlodipine monotherapy, reaching statistical significance with olmesartan/amlodipine 20/10 mg/day and 40/10 mg/day compared to amlodipine 10 mg/day (p=0.032 and 0=0.011, respectively). Two cases of drug-related hypotension were reported with olmesartan/amlodipine that resulted in discontinuation from the study. No differences in serum chemistry, hematology, or urinalysis parameters between treatment groups were observed (72).

Valsartan-amlodipine—Flack *et al* found that rates of peripheral edema with valsartan/ amlodipine combination (12.6%) were not different from amlodipine monotherapy (9.5%) (p = ns) (74). In a larger, better powered trial by Philipp *et al*, there was a significantly higher frequency of peripheral edema with amlodipine monotherapy than with combination therapy (73).

Telmisartan-amlodipine—In a double-blind, randomized trial by Neutel et al, drug-related adverse events were reported in 12.6% of patients with telmisartan/amlodipine 80/10 mg/day, 6.9% with telmisartan 80 mg/day, and 16.4% with amlodipine 10 mg/day. Reported serious adverse events were low in number (0.7% vs 0.9% and 0.9%, respectively). The frequency of peripheral edema was more common with amlodipine monotherapy compared with combination therapy (13.2 versus 9.3%, respectively) (75).

D. Safety of ARBs in combination with Diuretic and Amlodipine (Triple therapy)

There are 2 combination therapies with 3 antihypertensive agents that include an ARB (valsartan and olmesartan), thiazide diuretic and amlodipine (known as triple therapies). The most common reported adverse events with valsartan/amlodipine/HCTZ 320/10/25 mg/day were dizziness, headache and peripheral edema. Dizziness occurred more commonly with triple therapy and valsartan/HCTZ (320/25 mg/day) combination than with the component monotherapies, valsartan/amlodipine (320/10 mg/day) combination, and amlodipine/HCTZ (10/25 mg/day) combination. Peripheral edema occurred less frequently with triple therapy (4.5%) and valsartan/HCTZ (0.9%) compared with amlodipine/HCTZ (8.9%) or amlodipine/ valsartan (8.5%) (73).

Olmesartan/amlodipine/HCTZ is another triple combination medication approved for the treatment of hypertension. Oparil *et al* reported similar rates of dizziness between olmesartan/amlodipine/HCTZ 40/10/25 mg/day and olmesartan/HCTZ 40/25 mg/day but more often than olmesartan/amlodipine and amlodipine/HCTZ at maximum doses (9.9%, 10.0%, 4.9%, and 3.1%, respectively). Again, peripheral edema was more frequent in the amlodipine-containing regimen compared to other groups. The incidence of drug related adverse events were comparable between triple therapy and dual therapy. Twenty-three out of 574 (4.0%) patients in the triple therapy group withdrew from the study due to drug related adverse events. Hypotension occurred more frequently in the triple therapy than with olmesartan/HCTZ 40/25 mg/day, amlodipine/HCTZ 10/25 mg/day and olmesartan/ amlodipine 40/10 mg/day (2.1%, 0.7%, 0.2%, 0%, respectively). Dizziness and vertigo occurred in 11.3%, 10.7, 3.4%, and 5.5% of patients in each study group, respectively. Syncope was rare (< 1%) but was reported more with triple therapy (81).

X. SAFETY OF ARBs in OUTCOME STUDIES or ANALYSES

A. ARBs and Myocardial Infarction

After the VALUE trial in 2004 showed a statistically significant increased incidence of myocardial infarction in the valsartan arm, questions had been raised regarding the safety of ARBs. This unexpected relationship of ARBs with MI was coined the ARB-MI paradox. Strauss and Hall published a review article regarding this controversy and suggested that ARBs may be inferior to ACE inhibitors in preventing coronary heart disease. It was hypothesized that this could be a result of activation of AT_2 receptor due to AT_1 blockade resulting in cardiac fibrosis and hypertrophy. Other plausible mechanisms included higher levels of plasminogen activator inhibitor-1 and lower levels of bradykinin with ARBs use compared with ACE inhibitor use (119).

Results of two multicenter randomized controlled trials – ROADMAP (Randomized Olmesartan and Diabetes Microalbuminuria Prevention) and ORIENT (Olmesartan Reducing Incidence of End Stage Renal Diseae in Diabetic Nephropathy) showed increased cardiac death with olmesartan use (120–121). ROADMAP trial involving 4,447 diabetic patients without overt nephropathy but with one additional cardiovascular risk factor reported 15 cardiovascular deaths out of 2, 232 patients in the olmesartan arm compared to 3 deaths out of 2, 215 patients in the placebo arm (120). The ORIENT trial reported 10

cardiovascular deaths in the olmesartan group out of 282 patients and 3 deaths out of 284 patients in the placebo arm (121). The FDA initially released a statement indicating that benefit outweighs the risk with olmesartan use but after extensive safety review, they found no association between olmesartan and increased cardiovascular risk (122).

A meta-analysis by Cheung et al, which included 3 major trials with 29,375 patients in total – LIFE, SCOPE and VALUE, showed that ARBs are associated with increased risk of myocardial infarction [RR 1.12 (95% CI, 1.01 to 1.26), p=0.041] (123). On the other hand, another 3 studies showed neutral effect (124–126). However, in the most comprehensive and well-performed meta-analysis by Bangalore et al involving 37 trials with 147,020 patients in total, no evidence for increased risk of myocardial infarction (absolute increase of 0.3% corresponding to a number needed to harm of   333) was determined (127). In fact, conclusive evidence for relative risk reduction of stroke, heart failure and new onset diabetes with ARBs compared with controls was the key finding in this large analysis.

Hence, there is no evidence that ARB use increases the risk of myocardial infarction. Clearly, the benefits of ARBs have been demonstrated over the past 25 years in numerous clinical outcome trials.

B. ARBs and Cancer

In 2010, substantial controversy regarding the administration of ARBs causing certain solid cancers occurred following a meta-analysis of 9 trials in approximately 34,000 patients by Sipahi et al (8). This analysis showed an increased risk of new cancers in the ARB group [7.2% *vs* 6.0%, RR 1.08, (95% CI, 1.01 to 1.15), p=0.016] versus control therapy (placebo, ACE inhibitors, or beta blockers) with an absolute risk of 1.2% over an average of 4 years. Most of the patients in this study were derived from the OnTarget and Transcend programs that evaluated the ARB telmisartan. The meta-analysis also showed an increase in relative risk for the occurrence of new lung cancer in the ARB arms [RR 1.25, (95% CI, 1.05 to 1.49); p=0.01] driven in part by the losartan arm in the LIFE trial which showed a significantly higher occurrence of new lung cancer compared to atenolol [RR 2.41 (95% CI, 1.23 to 4.71), p=0.01].

In a much more comprehensive and well-performed meta-analysis on this topic, Bangalore and colleagues (9) pooled 70 randomized controlled trials with 324,168 participants with a mean follow-up of 3.5 years. Risk of developing cancer was not found to be different among ARBs [proportion with cancer = 2.04%; OR 1.01 (95% CI, 0.93 to 1.09)], ACE inhibitors [2.03%; OR 1.00 (95% CI, 0.91 to 1.09)], beta blockers [1.97%; OR 0.97 (95% CI, 0.88 to 1.07)], calcium channel blockers [2.11%; OR 1.05 (95% CI, 0.96 to 1.13)], or diuretics (2.02%; OR 1.00 (95% CI, 0.90 to 1.11)]. There were also no differences in cancer related mortality among the 4 antihypertensive therapy classes compared with placebo (9).

There were two observational studies (10, 128) that support the conclusions of the larger meta-analysis performed by Bangalore and colleagues (9). Pasternak et al (10) performed a large cohort study (1998–2006) involving 107,466 new users of ARBs and ACE inhibitors, at least 35 years of age using Danish registries to compare incidence rates of all cancer, cancer subgroups by anatomic site, and cancer mortality. Overall, 3954 cancer cases were

detected among ARBs users versus 6214 among ACE inhibitor users [adjusted rate ratio 0.99 (95% CI, 0.95 to 1.03)]. Cancer risk was not increased with increasing ARB exposure. In addition, none of the specific ARBs were associated with higher incidence of cancer compared with ACE inhibitor therapy. ARB use was not associated with increased risk of cancer mortality compared with ACE inhibitor use [adjusted RR, 0.77; (95% CI, 0.72 to 0.82)] (10). Another large cohort study involving 377,649 new ARB users of at least 18 years of age from UK General Practice Research Database assessed the association between ARBs and cancer risk (128). After a mean follow up of 4.6 years, ARB use was not found to increase the overall risk of cancer [adjusted HR 1.03 (95% CI, 0.99 to 1.06), p=0.10] versus ACE inhibitors. On the other hand, there was an increased risk of breast and prostate cancer which was translated to 0.5 to 1.1 extra cases, respectively, per 1000 person years of follow-up in those with the highest baseline cancer risk. Longer duration of ARB use was also not associated with higher overall cancer risk (128).

XI. CONCLUSIONS

The ARBs have proven to be a highly effective class of agents for the treatment of hypertension and its comorbidities over the past 2 decades. There are 8 ARBs approved for use in the USA for the treatment of hypertension (Table 2). As the ARBs were developed during the 1990s, they were accompanied by longer half-lives and in some cases greater potency that translated into enhanced BP reductions and/or durations of action. Combination therapy of ARBs with diuretics, calcium antagonists, and most recently, the beta-blocker nebivolol (129) showed better BP reduction in clinical trials than the monotherapy components. While there were theoretical benefits of combining ARBs with ACE inhibitors (e.g., proteinuria reduction), event-driven trials have not shown a benefit and in fact have demonstrated increases in adverse renal events. Hence, there is no clinical rationale for combining ARBs with ACE inhibitors (or direct renin inhibitors) in the management of hypertension. The excellent safety and tolerability profile of the ARB class has improved the adherence to antihypertensive therapy and enhanced our ability to manage hypertension in those patients with sensitivities to other antihypertensive drug classes, including the ACE inhibitors.

Acknowledgments

References

1. Data from the National Health and Nutrition Examination Survey (NHANES). National Center for Health Statistics. Health, United States, 2013: With Special Feature on Prescription Drugs. Hyattsville, MD: 2014. Downloaded from http://www.cdc.gov/nchs/data/hus/hus13.pdf#064

2. Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. JAMA. 2003; 289:2560–2572. [PubMed: 12748199]

3. James PA, Oparil S, Carter BL, et al. Evidence-based guideline for the management of high blood pressure in adults: Report from the Panel Members Appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014; 311:507–520. [PubMed: 24352797]

4. White WB, et al. Clinical practice guidelines for the management of hypertension in the community: a statement by the American Society of Hypertension and the International Society of Hypertension. J Clin Hypertens (Greenwich). 2014; 16:14–26. [PubMed: 24341872]

5. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension. Eur Heart J. 2013; 34:2159–2219. [PubMed: 23771844]

6. Dasgupta K, Quinn RR, Zarnke KB, et al. The 2014 Canadian Hypertension Education Program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. Can J Cardiol. 2014; 30:485–501. [PubMed: 24786438]

7. American Diabetes Association. Standards of medical care in diabetes-2013. Diabetes Care. 2013; 36(suppl 1):s11–s66. [PubMed: 23264422]

8. Sipahi I, Debanne SM, Rowland DY, Simon DI, Fang JC. Angiotensin-receptor blockade and risk of cancer: meta-analysis of randomised controlled trials. Lancet Oncol. 2010; 11:627–36. [PubMed: 20542468]

9. Bangalore S, Kumar S, Kjeldsen SE, et al. Antihypertensive drugs and risk of cancer: network meta-analyses and trial sequential analyses of 324,168 participants from randomised trials. Lancet Oncol. 2011; 12:65–82. [PubMed: 21123111]

10. Pasternak B, Svanström H, Callréus T, Melbye M, Hviid A. Use of angiotensin receptor blockers and the risk of cancer. Circulation. 201; 123:1729–36. [PubMed: 21482967]

11. Brenner, GM.; Stevens, CW. Pharmacology. 4. Philadelphia: Pennsylvania. Saunders; 2013.

12. Appel GB, Appel AS. Angiotensin II Receptor Antagonists: Role in Hypertension, Cardiovascular Disease, and Renoprotection. Prog Cardiovasc Dis. 2004; 47:105–15. [PubMed: 15586351]

13. Weir MR, Dzau VJ. The renin-angiotensin-aldosterone system: a specific target for hypertension management. Am J Hypertens. 1999; 12(12 Pt 3):205S–213S. [PubMed: 10619573]

14. Israili ZH. Clinical pharmacokinetics of angiotensin II (AT1) receptor blockers in hypertension. J Hum Hypertens. 2000; 14(Suppl 1):S73–S86. [PubMed: 10854085]

15. Brunner HR. Experimental and clinical evidence that angiotensin II is an independent risk factor for cardiovascular disease. Am J Cardiol. 2001; 87(8A):3C–9C.

16. Alderman MH, Madhavan S, Ooi WL, et al. Association of the renin-sodium profile with the risk of myocardial infarction in patients with hypertension. N Engl J Med. 1991; 324:1098–104. [PubMed: 1759997]

17. Burnier M. Angiotensin II Type 1 Receptor Blockers. Circulation. 2001; 103:904–912. [PubMed: 11171802]

18. Lauer D, Slavic S, Sommerfeld M, et al. Angiotensin type 2 receptor stimulation ameliorates left ventricular fibrosis and dysfunction via regulation of tissue inhibitor of matrix metalloproteinase 1/ matrix metalloproteinase 9 axis and transforming growth factor β1 in the rat heart. Hypertension. 2014; 63:e60–7. [PubMed: 24379181]

19. McClellan KJ, Balfour JA. Eprosartan. Drugs. 1998; 55:713–718. Discussion 719–720. [PubMed: 9585867]

20. Miura S, Karnik SS, Saku K. Review: Angiotensin II type 1 receptor blockers: class effects versus molecular effects. J Renin Angiotensin Aldosterone Syst. 2011; 12:1–7. [PubMed: 20603272]

21. White WB, Weber MA, 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. [PubMed: 21282560]

22. Cozaar: prescribing information. Merck Sharp & Dohme Corp; Whitehouse Station: Updated 2013Retrieved from http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020386s060lbl.pdf

23. Diovan: prescribing information Updated 2014. Novartis Pharmaceuticals Corp; East Hanover, NJ: Retrieved from http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020665s034s035lbl.pdf

24. Atacand: prescribing information. Takeda Pharmaceutical Company; Wilmington, DE: Updated 2013Retrieved from http://www1.astrazeneca-us.com/pi/Atacand.pdf

25. Avapro: prescribing information. Sanofi-aventis; Bridgewater, NJ: Updated 2014Retrieved from http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020757s064lbl.pdf

26. Benicar: prescribing information. Daiichi Sankyo; Parsippany, New Jersey: Updated 2014http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021286s031lbl.pdf

27. Micardis: prescribing information. Boehringer Ingelheim; Ridgefield, CT: Updated 2012http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020850s033lbl.pdf

28. Teveten: prescribing information. Abbott Laboratories; North Chicago, Illinois: Updated 2011http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020738s026lbl.pdf

29. Edarbi: prescribing information. Takeda Pharmaceutical Company; Deerfield, IL: Updated 2011http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/200796s000lbl.pdf

30. Song JC, White CM. Pharmacologic, pharmacokinetic, and therapeutic differences among angiotensin II receptor antagonists. Pharmacotherapy. 2000; 20:130–9. [PubMed: 10678291]

31. Hübner R, Högemann AM, Sunzel M, et al. Pharmacokinetics of candesartan after single and repeated doses of candesartan cilexetil in young and elderly healthy volunteers. J Hum Hypertens. 1997; 11 (Suppl 2):S19–25. [PubMed: 9331000]

32. Scott LJ, McCormack PL. Olmesartan Medoxomil A Review of its Use in the Management of Hypertension. Drugs. 2008; 68:1239–1272. [PubMed: 18547134]

33. Derosa G, Ragonesi PD, Mugellini A, Ciccarelli L, Fogari R. Effects of telmisartan compared with eprosartan on blood pressure control, glucose metabolism and lipid profile in hypertensive, type 2 diabetic patients: a randomized, double-blind, placebo-controlled 12-month study. Hypertens Res. 2004; 27:457–64. [PubMed: 15302981]

34. Brunner HR. The new angiotensin II receptor antagonist, irbesartan: pharmacokinetic and pharmacodyn-amic considerations. Am J Hypertens. 1997; 10:311S–317S. [PubMed: 9438775]

35. Sharpe M, Jarvis B, Goa KL. Telmisartan A review of its use in hypertension. Drugs. 2001; 61:1501–1529. [PubMed: 11558835]

36. Chang C, Bahadduri PM, et al. Rapid identification of P-glycoprotein substrates and Inhibitors. Drug Metab Dispos. 2006; 34:1976–84. [PubMed: 16997908]

37. Black HR, Bailey J, Zappe D, Samuel R. Valsartan: More than a decade of experience. Drugs. 2009; 69:2393–2414. [PubMed: 19911855]

38. Andersson OK, Neldam S. The antihypertensive effect and tolerability of candesartan cilexetil, a new generation angiotensin II antagonist, in comparison with losartan. Blood Press. 1998; 7:53–9. [PubMed: 9551878]

39. Lacourcière Y, Asmar R. A comparison of the efficacy and duration of action of candesartan cilexetil and losartan as assessed by clinic and ambulatory blood pressure after a missed dose, in truly hypertensive patients: a placebo-controlled, forced titration study. Candesartan/Losartan study investigators. Am J Hypertens. 1999; 12:1181–7. [PubMed: 10619580]

40. Gradman AH, Lewin A, Bowling BT, et al. Comparative effects of candesartan cilexetil and losartan in patients with systemic hypertension. Candesartan Versus Losartan Efficacy Comparison (CANDLE) Study Group. Heart Dis. 1999; 1:52–7. [PubMed: 11720604]

41. Manolis AJ, Grossman E, Jelakovic B, et al. Effects of losartan and candesartan monotherapy and losartan/hydrochlorothiazide combination therapy in patients with mild to moderate hypertension. Losartan Trial Investigators. Clin Ther. 2000; 22:1186–203. [PubMed: 11110230]

42. Vidt DG, White WB, Ridley E, et al. A forced titration study of antihypertensive efficacy of candesartan cilexetil in comparison to losartan: CLAIM Study II. J Hum Hypertens. 2001; 15:475–80. [PubMed: 11464257]

43. Brunner HR, Stumpe KO, Januszewicz A. Antihypertensive efficacy of olmesartan medoxomil and candesartan cilexetil assessed by 24-hour ambulatory blood pressure monitoring in patients with essential hypertension. Clin Drug Invest. 2003; 23:419–30.

44. Oparil S, Williams D, Chrysant SG, Marbury TC, Neutel J. Comparative efficacy of olmesartan, losartan, valsartan, and irbesartan in the control of essential hypertension. J Clin Hypertens (Greenwich). 2001; 3:283–91. 318. [PubMed: 11588406]

45. Giles TD, Oparil S, Silfani TN, Wang A, Walker JF. Comparison of increasing doses of olmesartan medoxomil, losartan potassium, and valsartan in patients with essential hypertension. J Clin Hypertens (Greenwich). 2007; 9:187–95. [PubMed: 17341994]

46. Lee YT, Lee CM, Lin CS, et al. A double-blind comparison of the efficacy and tolerability of telmisartan 40–80 mg vs. losartan 50–100 mg in Taiwanese hypertensive patients. Int J Clin Pract (Suppl). 2004; 145:40–5. [PubMed: 15617458]

47. Mallion J, Siche J, Lacourcière Y. ABPM comparison of the antihypertensive profiles of the selective angiotensin II receptor antagonists telmisartan and losartan in patients with mild-to-moderate hypertension. J Hum Hypertens. 1999; 13:657–64. [PubMed: 10516734]

48. Zhu JR1, Bai J, Cai NS, et al. Efficacy and safety of telmisartan vs. losartan in control of mild-to-moderate hypertension: a multicentre, randomised, double-blind study. Int J Clin Pract (Suppl). 2004; 145:46–9. [PubMed: 15617459]

49. Calvo C, Hermida RC, Ayala DE, Ruilope LM. Effects of telmisartan 80 mg and valsartan 160 mg on ambulatory blood pressure in patients with essential hypertension. J Hypertens. 2004; 22:837–46. [PubMed: 15126927]

50. White WB, Lacourciere Y, Davidai G. Effects of the angiotensin II receptor blockers telmisartan versus valsartan on the circadian variation of blood pressure: impact on the early morning period. Am J Hypertens. 2004; 17:347–53. [PubMed: 15062889]

51. Kassler-Taub K, Littlejohn T, Elliott W, Ruddy T, Adler E. Comparative efficacy of two angiotensin II receptor antagonists, irbesartan and losartan in mild-to-moderate hypertension. Irbesartan/Losartan Study Investigators. Am J Hypertens. 1998; 11:445–53. [PubMed: 9607383]

52. Mancia G, Korlipara K, van Rossum P, Villa G, Silvert B. An ambulatory blood pressure monitoring study of the comparative antihypertensive efficacy of two angiotensin II receptor antagonists, irbesartan and valsartan. Blood Press Monit. 2002; 7:135–42. [PubMed: 12048432]

53. 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; 57:413–20. [PubMed: 21282560]

54. Sica D, White WB, Weber MA, et al. Comparison of the novel angiotensin II receptor blocker azilsartan medoxomil vs valsartan by ambulatory blood pressure monitoring. J Clin Hypertens (Greenwich). 2001; 13:467–72. [PubMed: 21762358]

55. Bakris G, Gradman A, et al. CLAIM Study Investigators. Antihypertensive efficacy of candesartan in comparison to losartan: the CLAIM study. J Clin Hypertens (Greenwich). 2001; 3:16–21. [PubMed: 11416677]

56. Littlejohn T, Mroczek W, Marbury T, VanderMaelen CP, Dubiel RF. A prospective, randomized, open-label trial comparing telmisartan 80 mg with valsartan 80 mg in patients with mild to moderate hypertension using ambulatory blood pressure monitoring. Can J Cardiol. 2000; 16:1123–32. [PubMed: 11021956]

57. White WB, Anwar YA, Mansoor GA, Sica DA. Evaluation of the 24-hour blood pressure effects of eprosartan in patients with systemic hypertension. Am J Hypertens. 2001; 14:1248–55. [PubMed: 11775134]

58. Waeber B. Combination therapy with ACE inhibitors/angiotensin II receptor antagonists and diuretics in hypertension. Expert Rev Cardiovasc Ther. 2003; 1:43–50. [PubMed: 15030296]

59. Sica DA, Carter B, Cushman W, Hamm L. Thiazide and loop diuretics. J Clin Hypertens (Greenwich). 2011; 13:639–43. [PubMed: 21896142]

60. Fogari R, Zoppi A, Derosa G, et al. Effect of valsartan addition to amlodipine on ankle oedema and subcutaneous tissue pressure in hypertensive patients. J Hum Hypertens. 2007; 21:220–4. [PubMed: 17215848]

61. Bönner G, Landers B, Bramlage P. Candesartan cilexetil/hydrochlorothiazide combination treatment versus high-dose candesartan cilexetil monotherapy in patients with mild to moderate cardiovascular risk (CHILI Triple T). Vasc Health Risk Manag. 2011; 7:85–95. [PubMed: 21415922]

62. Sachse A, Verboom CN, Jäger B. Efficacy of eprosartan in combination with HCTZ in patients with essential hypertension. J Hum Hypertens. 2002; 16:169–76. [PubMed: 11896506]

63. Rosenbaum D, Girerd X. Olmesartan medoxomil combined with hydrochlorothiazide improves 24-hour blood pressure control in moderate-to-severe hypertension. Curr Med Res Opin. 2012; 28:179–86. [PubMed: 22114906]

64. Saruta T, Ogihara T, Matsuoka H, et al. Antihypertensive efficacy and safety of fixed-dose combination therapy with losartan plus hydrochlorothiazide in Japanese patients with essential hypertension. Hypertens Res. 2007; 30:729–39. [PubMed: 17917321]

65. Salerno CM, Demopoulos L, Mukherjee R, Gradman AH. Combination angiotensin receptor blocker/hydrochlorothiazide as initial therapy in the treatment of patients with severe hypertension. J Clin Hypertens (Greenwich). 2004; 6:614–20. [PubMed: 15538094]

66. Neutel JM, Franklin SS, Lapuerta P, et al. A comparison of the efficacy and safety of irbesartan/ HCTZ combination therapy with irbesartan and HCTZ monotherapy in the treatment of moderate hypertension. J Hum Hypertens. 2008; 22:266–74. [PubMed: 17928878]

67. Calhoun DA, Glazer RD, Pettyjohn FS, et al. Efficacy and tolerability of combination therapy with valsartan/hydrochlorothiazide in the initial treatment of severe hypertension. Curr Med Res Opin. 2008; 24:2303–11. [PubMed: 18593517]

68. Lacourcière Y, Martin K. Comparison of a fixed-dose combination of 40 mg telmisartan plus 12.5 mg hydrochlorothiazide with 40 mg telmisartan in the control of mild to moderate hypertension. Am J Ther. 2002; 9:111–7. [PubMed: 11897925]

69. Lacourcière Y, Tytus R, O'Keefe D, et al. Efficacy and tolerability of a fixed-dose combination of telmisartan plus hydrochlorothiazide in patients uncontrolled with telmisartan monotherapy. J Hum Hypertens. 2001; 15:763–70. [PubMed: 11687919]

70. Neldam S, Edwards C. Results of increasing doses of hydrochlorothiazide in combination with an angiotensin receptor blocker in patients with uncontrolled hypertension. J Clin Hypertens (Greenwich). 2008; 10:612–8. [PubMed: 18772643]

71. Sica D, Bakris GL, White WB, et al. Blood pressure-lowering efficacy of the fixed-dose combination of azilsartan medoxomil and chlorthalidone: a factorial study. J Clin Hypertens (Greenwich). 2012; 14:284–92. [PubMed: 22533654]

72. Chrysant SG, Melino M, Karki S, Lee J, Heyrman R. The combination of olmesartan medoxomil and amlodipine besylate in controlling high blood pressure: COACH, a randomized, double-blind, placebo-controlled, 8-week factorial efficacy and safety study. Clin Ther. 2008; 30:587–604. [PubMed: 18498909]

73. Philipp T, Smith TR, Glazer R, et al. Two multicenter, 8-week, randomized, double-blind, placebo-controlled, parallel-group studies evaluating the efficacy and tolerability of amlodipine and valsartan in combination and as monotherapy in adult patients with mild to moderate essential hypertension. Clin Ther. 2007; 29:563–80. [PubMed: 17617280]

74. Flack JM, Calhoun DA, Satlin L, et al. Efficacy and safety of initial combination therapy with amlodipine/valsartan compared with amlodipine monotherapy in black patients with stage 2 hypertension: the EX-STAND study. J Hum Hypertens. 2009; 23:479–89. [PubMed: 19190658]

75. Neutel JM, Mancia G, Black HR, et al. Single-pill combination of telmisartan/amlodipine in patients with severe hypertension: results from the TEAMSTA severe HTN study. J Clin Hypertens (Greenwich). 2012; 14:206–15. [PubMed: 22458741]

76. Hong BK, Park CG, Kim KS, et al. Comparison of the efficacy and safety of fixed-dose amlodipine/losartan and losartan in hypertensive patients inadequately controlled with losartan: a randomized, double-blind, multicenter study. Am J Cardiovasc Drugs. 2012; 12:189–95. [PubMed: 22462558]

77. Rakugi H, Ogihara T, Miyata Y, Sasai K, Totsuka N. Evaluation of the efficacy and tolerability of combination therapy with candesartan cilexetil and amlodipine besilate compared with candesartan cilexetil monotherapy and amlodipine besilate monotherapy in Japanese patients with mild-to-moderate essential hypertension: a multicenter, 12-week, randomized, double-blind, placebo-controlled, parallel-group study. Clin Ther. 2012; 34:838–48. [PubMed: 22440192]

78. Calhoun DA, Lacourcière Y, Crikelair N, Jia Y, Glazer RD. Effects of demographics on the antihypertensive efficacy of triple therapy with amlodipine, valsartan, and hydrochlorothiazide for moderate to severe hypertension. Curr Med Res Opin. 2013; 29:901–10. [PubMed: 23721363]

79. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA. 2002; 288:2981–97. [PubMed: 12479763]

80. Calhoun DA, Lacourcière Y, Chiang YT, Glazer RD. Triple antihypertensive therapy with amlodipine, valsartan, and hydrochlorothiazide: a randomized clinical trial. Hypertension. 2009; 54:32–9. [PubMed: 19470877]

81. Oparil S, Melino M, Lee J, Fernandez V, Heyrman R. 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; 32:1252–69. [PubMed: 20678674]

82. Roth EM, Oparil S, Melino M, Lee J, Fernandez V, Heyrman R. Olmesartan/amlodipine/hydrochlorothiazide in obese participants with hypertension: a TRINITY subanalysis. J Clin Hypertens (Greenwich). 2013; 15:584–92. [PubMed: 23889722]

83. Chrysant SG, Littlejohn T 3rd, Izzo JL Jr, et al. Triple-Combination therapy with olmesartan, amlodipine, and hydrochlorothiazide in black and non-black study participants with hypertension: the TRINITY randomized, double-blind, 12-week, parallel-group study. Am J Cardiovasc Drugs. 2012; 12:233–43. [PubMed: 22799613]

84. Chrysant SG, Izzo JL Jr, Kereiakes DJ, Littlejohn T 3rd, Oparil S, et al. Efficacy and safety of triple-combination therapy with olmesartan, amlodipine, and hydrochlorothiazide in study participants with hypertension and diabetes: a subpopulation analysis of the TRINITY study. J Am Soc Hypertens. 2012; 6:132–41. [PubMed: 22030597]

85. Makani H, Bangalore S, Desouza KA, Shah A, Messerli FH. Efficacy and safety of dual blockade of the renin-angiotensin system: meta-analysis of randomised trials. BMJ. 2013; 346:360.

86. 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; 372:547–53. [PubMed: 18707986]

87. Parving HH, Brenner BM, McMurray JJ, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. N Engl J Med. 2012; 367:2204–13. [PubMed: 23121378]

88. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004; 364:937–52. [PubMed: 15364185]

89. Dahlöf B, Devereux RB, Kjeldsen SE, et al. LIFE Study Group. 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. [PubMed: 11937178]

90. Julius S, Kjeldsen SE, Brunner H, et al. VALUE trial: Long-term blood pressure trends in 13,449 patients with hypertension and high cardiovascular risk. Am J Hypertens. 2003; 16:544–8. [PubMed: 12850387]

91. 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; 21:875–86. [PubMed: 12714861]

92. Yusuf S, Teo K, Anderson C, Pogue J, et al. Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND) Investigators. 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; 372:1174–83. [PubMed: 18757085]

93. Parving HH, Lehnert H, Bröchner-Mortensen J, Gomis R, Andersen S, Arner P. Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med. 2001; 345:870–8. [PubMed: 11565519]

94. Viberti G, Wheeldon NM. Microalbuminuria Reduction With Valsartan (MARVAL) Study Investigators. Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus: a blood pressure-independent effect. Circulation. 2002; 106:672–8. [PubMed: 12163426]

95. 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; 345:861–9. [PubMed: 11565518]

96. 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; 345:851–60. [PubMed: 11565517]

97. Pitt B, Poole-Wilson PA, Segal R, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial--the Losartan Heart Failure Survival Study ELITE II. Lancet. 2000; 355:1582–7. [PubMed: 10821361]

98. Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med. 2003; 349:1893–906. [PubMed: 14610160]

99. Dickstein K, Kjekshus J. OPTIMAAL Steering Committee of the OPTIMAAL Study Group. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan. Lancet. 2002; 360:752–60. [PubMed: 12241832]

100. Pfeffer MA, Swedberg K, Granger CB, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. Lancet. 2003; 362:759–66. [PubMed: 13678868]

101. Granger CB, McMurray JJ, Yusuf S, et al. CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet. 2003; 362:772–6. [PubMed: 13678870]

102. McMurray JJ, Ostergren J, Swedberg K, et al. CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. Lancet. 2003; 362:767–71. [PubMed: 13678869]

103. Yusuf S, Pfeffer MA, Swedberg K, et al. CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet. 2003; 362:777–81. [PubMed: 13678871]

104. Cohn JN, Tognoni G. Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med. 2001; 345:1667–75. [PubMed: 11759645]

105. Massie BM, Carson PE, McMurray, et al. I-PRESERVE Investigators. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med. 2008; 359:2456–67. [PubMed: 19001508]

106. Visser LE, Stricker BH, van der Velden J, Paes AH, Bakker A. Angiotensin converting enzyme inhibitor associated cough: a population-based case-control study. J Clin Epidemiol. 1995; 48:851–7. [PubMed: 7769416]

107. Israili ZH, Hall WD. Cough and angioneurotic edema associated with angiotensin-converting enzyme inhibitor therapy. A review of the literature and pathophysiology. Ann Intern Med. 1992; 117:234–42. [PubMed: 1616218]

108. Caldeira D, David C, Sampaio C. Tolerability of angiotensin-receptor blockers in patients with intolerance to angiotensin-converting enzyme inhibitors: a systematic review and meta-analysis. Am J Cardiovasc Drugs. 2012; 12:263–77. [PubMed: 22587776]

109. Rubio-Tapia A, Herman ML, Ludvigsson JF, et al. Severe spruelike enteropathy associated with olmesartan. Mayo Clin Proc. 2012; 87:732–8. [PubMed: 22728033]

110. FDA Drug Safety Communication. FDA approves label changes to include intestinal problems (sprue-like enteropathy) linked to blood pressure medicine olmesartan medoxomil. Retrieved from http://www.fda.gov/downloads/Drugs/DrugSafety/UCM359496.pdf

111. Greywoode R, Braunstein E, Arguelles-Grande C, et al. Olmesartan, other antihypertensives, and chronic diarrhea among patients undergoing endoscopic procedures: a case-control study. Mayo Clin Proc. 2014; 89:1239–43. [PubMed: 25023670]

112. Fujiwara W, Izawa H, Ukai G, et al. Low dose of hydrochlorothiazide, in combination with angiotensin receptor blocker, reduces blood pressure effectively without adverse effect on glucose and lipid profiles. Heart Vessels. 2013; 28:316–22. [PubMed: 22447467]

113. Mengden T, Hübner R, Bramlage P. Office and ambulatory blood pressure control with a fixed-dose combination of candesartan and hydrochlorothiazide in previously uncontrolled hypertensive patients: results of CHILI CU Soon. Vasc Health Risk Manag. 2011; 7:761–9. [PubMed: 22241950]

114. Fogari R, Taddei S, Holm-Bentzen M, et al. Efficacy and safety of olmesartan medoxomil 40mg/hydrochlorothiazide12. 5mg combination therapy versus olmesartan medoxomil 40mg monotherapy in patients with moderate to severe hypertension. Clin Drug Invest. 2010; 30:581–597.

115. Lapuerta P, Franklin S. The risks and benefits of initial irbesartan/hydrochlorothiazide combination therapy in patients with severe hypertension. J Clin Hypertension. 2009; 11:277–283.

116. Pool JL, Glazer R, Weinberger M, et al. Comparison of valsartan/hydrochlorothiazide combination therapy at doses up to 320/25 mg versus monotherapy: A double-blind, placebo-controlled study followed by long-term combination therapy in hypertensive adults. Clin Ther. 2007; 29:61–73. [PubMed: 17379047]

117. Weir M, Crikelair N, Levy D. Evaluation of the dose response with valsartan and valsartan/hydrochlorothiazide in patients with essential hypertension. J Clin Hypertens. 2007; 9:103–112.

118. White WB, Calhoun D, Samuel R, et al. Improving blood pressure control: Increase the dose of diuretic or switch to a fixed-dose angiotensin receptor blocker/diuretic? The Valsartan Hydrochlorothiazide Diuretic for Initial Control and Titration to Achieve Optimal Therapeutic Effect (Val-DICTATE) Trial. J Clin Hypertens (Greenwich). 2008; 10:450–458. [PubMed: 18550935]

119. Strauss MH, Hall AS. Angiotensin receptor blockers may increase risk of myocardial infarction: unraveling the ARB-MI paradox. Circulation. 2006; 114:838–54. [PubMed: 16923768]

120. Haller H, Ito S, Izzo JL Jr, Januszewicz A, et al. ROADMAP Trial Investigators. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. N Engl J Med. 2011; 364:907–17. [PubMed: 21388309]

121. Imai E, Chan JC, Ito S, et al. Effects of olmesartan on renal and cardiovascular outcomes in type 2 diabetes with overt nephropathy: a multicentre, randomised, placebo-controlled study. Diabetologia. 2011; 54:2978–86. [PubMed: 21993710]

122. FDA Drug Safety Communication. FDA review of cardiovascular risks for diabetics taking hypertension drug olmesartan not conclusive; label updates required. Retrieved from http://www.fda.gov/Drugs/DrugSafety/ucm402323.htm

123. Cheung BM, Cheung GT, Lauder IJ, Lau CP, Kumana CR. Meta-analysis of large outcome trials of angiotensin receptor blockers in hypertension. J Hum Hypertens. 2006; 20:37–43. [PubMed: 16121197]

124. Verdecchia P, Angeli F, Gattobigio R, Reboldi GP. Do angiotensin II receptor blockers increase the risk of myocardial infarction? Eur Heart J. 2005; 26:2381–6. [PubMed: 16081468]

125. McDonald MA, Simpson SH, Ezekowitz JA, Gyenes G, Tsuyuki RT. Angiotensin receptor blockers and risk of myocardial infarction: systematic review. BMJ. 2005; 331:873. (online pub only). [PubMed: 16183653]

126. Volpe M, Mancia G, Trimarco B. Angiotensin II receptor blockers and myocardial infarction: deeds and misdeeds. J Hypertens. 2005; 23:2113–8. [PubMed: 16269950]

127. Bangalore S, Kumar S, Wetterslev J, Messerli FH. Angiotensin receptor blockers and risk of myocardial infarction: meta-analyses and trial sequential analyses of 147 020 patients from randomised trials. BMJ. 2011; 342:d2234. [PubMed: 21521728]

128. Bhaskaran K, Douglas I, Evans S, van Staa T, Smeeth L. Angiotensin receptor blockers and risk of cancer: cohort study among people receiving antihypertensive drugs in UK General Practice Research Database. BMJ. 2012; 344:e2697. [PubMed: 22531797]

129. Giles TD, Weber MA, Basile J, et al. Efficacy and safety of nebivolol and valsartan as fixed-dose combination in hypertension: a randomized, multicenter study. Lancet. 2014; 383:1889–98. [PubMed: 24881993]

130. Yusuf S, Diener H, Sacco RL, et al. Telmisartan to prevent recurrent stroke and cardiovascular events. N Engl J Med. 2008; 359:1225–37. [PubMed: 18753639]

Key Findings

ARBs are effective initial antihypertensive therapies that both lower blood pressure and have pleomorphic effects. They have proven benefits in diabetic kidney disease, stroke prevention, and heart failure. The safety and tolerability profiles of the ARBs are among the best for antihypertensive drugs and comparisons of agents within the class are similar.

Table 1

Pharmacologic Characteristics of the Angiotensin Receptor Blockers

ARBs	Half-life (h)	Tmax (h)	Bioavailability	Route of elimination: renal (R) biliary/fecal (B)	Food Interaction	Drug Interactions$^\varphi$	CYP metabolism
Losartan [*]	2	1–1.5	33%	35% R; 60% B	Yes$^\infty$	Rifampin, fluconazole	2C9, 3A4
Candesartan cilexetil	9	2–5$^\varepsilon$	42%	33% R; 67% B	No	None	2C9 (negligible)
Eprosartan	5–9	1–3	63%	7% R; 90% B	Yes¶	None	No
Irbesartan	11–15	1.3–3	60–80%	20% R; 80% B	No		2C9, 3A4 (negligible)
Telmisartan	24	0.5–1	43%	<1% R; >97% B	No	Digoxin	No
Valsartan	6	2–4	23% (capsule) 50% (solution)	13% R; 83% B	Yes§	None	2C9 (weak)
Olmesartan medoxomil	12–14	1.7–2.5	26%	35–50%R; 50–65% B	No	None	No
Azilsartan medoxomil	12	1.5–3	60%	42% urine; 55% B	No	None	2C9, CYP2B6 (negligible), CYP2C8 (negligible)

$^\varphi$Co-administration of ARBs with lithium increases lithium toxicity due to increase renal absorption of lithium

[*]
Losartan is converted to EXP-3174 with terminal half-life of 6–9 hours and Tmax of 4–6 hours.

$^\infty$Food delays absorption and lowers its C$_{max}$ but the AUC of it and EXP-3174 are not significantly altered.

$^\varepsilon$Tmax of candesartan, its active metabolite.

§40–50% reduction in bioavailability.

¶High fat food increases bioavailability by 80% and AUC by 55% but slows gut absorption

Table 2

Doses for Hypertension and Other Indications of the Angiotensin Receptor Blockers

ARBs	Starting dose (mg/day)[ψ]	Maximum dose (mg/day)	Dosing interval	Other Indications Approved Outside of Hypertension
Losartan (22)	50	100	Once a day or twice a day	Diabetic nephropathy when serum creatinine is increased and proteinuria present in patients with hypertension and type 2 diabetes; Stroke reduction in patients with hypertension and left ventricular hypertrophy (non-black only)
Candesartan cilexetil (24)	16[*]	32	Once a day or twice a day	Treatment of heart failure (NYHA Classes II–IV)
Eprosartan (28)	600	800	Once a day or twice a day	None
Irbesartan (25)	150[*]	300	Once a day	Diabetic nephropathy when serum creatinine is increased and proteinuria present in patients with hypertension and type 2 diabetes
Telmisartan (27)	40[*]	80	Once a day	Cardiovascular risk reduction in patients unable to take ACE inhibitors
Valsartan (23)	80 or 160	320	Once a day	Treatment of heart failure (NYHA Classes II–IV); Reduction of CV mortality in clinically stable patients with left ventricular failure or dysfunction following myocardial infarction.
Olmesartan medoxomil (26)	20[*]	40	Once a day	None
Azilsartan medoxomil (29)	40 or 80	80	Once a day	None

NYHA – New York Heart Association; lower starting doses are typically initiated for the indication of heart failure (candesartan and valsartan) in twice daily regimens.

[ψ]Recommended starting monotherapy dose in the absence of dehydration

[*] Lower doses for initial therapy are available for patients with renal dysfunction, including older persons

Table 3

Blood Pressure Reductions in Randomized Controlled Trials of Angiotensin Receptor Antagonists

Study and Year	Duration (weeks)	Titration type	Drug	Dosage (mg)	Sample size (n)	Mean baseline blood pressure (mmHg)	Mean BP reduction (mmHg)
CANDESARTAN (CAN) versus other ARBs							
Andersson (38) 1998	8	None	Candesartan	8	77	169/102	16*/9*
			Candesartan	16	80	168/103	17*/10*
			Losartan	50	74	168/104	15/9
Gradman et al (40) 1999	8	Optional	Candesartan	16–32	160	153/100	12/11
			Losartan	50–100	169	154/101	10/9
Lacourciere and Asmar (39) 1999	8	Forced	Candesartan	8/16	106	162/101	13¶*/9*
			Losartan	50/100	100	161/100	9*/7*
Manolis et al (41) 2000	12	Optional	Candesartan	8–16	462	153/100	16/13
			Losartan	50–100	449	153/100	14/12
Vidt et al (42) 2001	8	Forced	Candesartan	16/32	306	154/100	13¶/11¶
			Losartan	50/100	303	152/100	10/9
Bakris et al (55) 2001	8	Forced	Candesartan	16/32	319	152/100	13¶/11¶
			Losartan	50/100	303	152/100	10/9
OLMESARTAN (OLM) versus other ARBs							
Oparil et al (44) 2001	8	None	Olmesartan	20	145	157/104	13¶/9¶
			Irbesartan	150	145	156/104	11/7
			Valsartan	80	142	155/104	8/6
			Losartan	50	146	157/104	9/6
Brunner et al (43) 2003	8	None	Olmesartan	20	312	162/104	21/16
			Candesartan	8	323	162/104	21/15
Giles et al (45) 2007	12	Forced	Olmesartan	20/40	182	155/103	14/12
			Losartan	50/100	180	155/103	13/12
			Valsartan	80/320	181	154/103	15/12
TELMISARTAN (TEL) versus other ARBs							

Study and Year	Duration (weeks)	Titration type	Drug	Dosage (mg)	Sample size (n)	Mean baseline blood pressure (mmHg)	Mean BP reduction (mmHg)
Mallion (47) 1999	6	None	Telmisartan	40	57	162/101	14*/9*
			Telmisartan	80	54	164/102	16¶/10¶
			Losartan	50	57	162/100	10*/6
Lee et al (46) 2004	4	Optional	Telmisartan	40–80	86	154/101	17¶/9
			Losartan	50–100	90	155/102	14/9
Derosa et al (33) 2004	54	None	Telmisartan	40	40	143/92	8*/8*
			Eprosartan	600	39	144/91	7*/4*
Zhu et al (48) 2004	8	Optional	Telmisartan	40–80	164	149/99	13¶/11¶
			Losartan	50–100	166	165/100	9/9
Calvo et al (49) 2004	12	None	Telmisartan	80	34	152/89	11/8
			Valsartan	160	36	157/92	19¶/12¶
White et al (50) 2004	8	Forced	Telmisartan	40/80	244	154/99	12/8
			Valsartan	80/160	246	153/99	11/7
IRBESARTAN (IRB) versus other ARBs							
Kassler_Taub et al (51) 1998	8	None	Irbesartan	150	129	155/101	12*/10*
			Irbesartan	300	134	155/100	16*¶/12*¶
			Losartan	100	131	153/100	11*/9*
Mancia et al (52) 2002	8	None	Irbesartan	150	211	159/101	16¶/11¶
			Valsartan	80	215	158/101	10/7
AZILSARTAN (AZL) versus other ARBs							
White et al (53) 2011	6	None	Azilsartan	40	280	157/93	13*¶ (vs VAL only)
			Azilsartan	80	285	158/92	15¶ (vs both VAL and OLM)
			Valsartan	320	282	157/93	10*
			Olmesartan	40	290	158/92	12*
Sica et al (54) 2011	24	Forced	Azilsartan	20/40	327	158/91	15¶
			Azilsartan	20/80	329	158/92	17¶

Study and Year	Duration (weeks)	Titration type	Drug	Dosage (mg)	Sample size (n)	Mean baseline blood pressure (mmHg)	Mean BP reduction (mmHg)
			Valsartan	80/320	328	157/91	12

*
statistically significant versus placebo

¶statistically significant versus ARB comparator

Italicized values are mean 24-hour ambulatory blood pressure reduction readings

Table 4

Blood Pressure Reductions in Randomized Controlled Trials of Angiotensin Receptor Antagonists/Diuretic Combinations versus Component Monotherapy

Study and Year	Duration (weeks)	Drug	Dose (mg)	Sample size (n)	Mean baseline blood pressure (mmHg)	Mean BP reduction (mmHg) from baseline
CANDESARTAN (CAN)/HCTZ versus component monotherapy						
Bönner et al 2011 (61)	12	CAN + HCTZ	16+12.5	3337	160/95	29/14
		CAN	32	1263	162/95	30/4
EPROSARTAN (EPR)/HCTZ versus component monotherapy						
Sachse et al 2002 (62)	8	EPR+HCTZ	600+12.5	152	155/100	12¶/11¶ (vs EPR 600)
		EPR	600	157	156/99	9/8
OLMESARTAN (OLM)/HCTZ versus component monotherapy						
Rosenbaum et al 2012 (63)*	8	OLM+HCTZ	20+12.5	262	156/97	7¶/4¶ (vs OLM 40)
		OLM+HCTZ	20+25	474	153/97	12¶/8¶ (vs OLM 40)
		OLM+HCTZ	40+12.5	263	154/98	9¶/5¶ (vs OLM 40)
		OLM+HCTZ	40+25	607	154/97	14¶/9¶ (vs OLM 40)
		OLM	40	264	156/97	3/2
LOSARTAN (LOS)/HCTZ versus component monotherapy						
Saruta et al 2007 (64)	8	LOS+HCTZ	50+12.5	154	154/101	18¶/13¶ (vs both LOS 50 and HCTZ 12.5)
		LOS+HCTZ	50+6.25	159	155/101	15¶/10¶ (vs HCTZ 12.5)
		LOS+HCTZ	25+6.25	153	155/101	14/10
		LOS	50	157	154/101	10/9
		HCTZ	12.5	162	155/100	12/8
Salerno et al 2004 (65)€	6	LOS+HCTZ	50/100+12.5/25	393	171/113	25¶/18¶ (vs LOS 100)
		LOS	50/100	192	171/113	14/12
IRBESARTAN (IRB)/HCTZ versus component monotherapy						
Neutel et al 2008 (66)€	8	IRB+HCTZ	150/300+12.5/25	303	162/98	27¶/15¶ (vs both IRB 300 and HCTZ 25)
		IRB	150/300	95	161/98	22/12
		HCTZ	12.5/25	95	162/98	16/7

Study and Year	Duration (weeks)	Drug	Dose (mg)	Sample size (n)	Mean baseline blood pressure (mmHg)	Mean BP reduction (mmHg) from baseline
VALSARTAN (VAL)/HCTZ versus component monotherapy						
Calhoun et al 2008 (67) €	6	VAL+HCTZ	160/320+12.5/25	307	169/112	33¶/24¶(vs VAL 320)
		VAL	160/320	301	168/112	24/18
TELMISARTAN (TEL)/HCTZ versus component monotherapy						
Lacourciere and Martin 2002 (68)	8	TEL+HCTZ	40+12.5	159	147/96	11¶/7¶ (vs TEL 40)
		TEL	40	162	147/96	3/4
Lacourciere et al 2001 (69)	8	TEL+HCTZ	80/12.5	246	149/96	13¶/8¶¶ (vs TEL 80)
		TEL	80	245	149/97	7/5
Neldam et al 2008 (70)	8	TEL+HCTZ	80/12.5	361	148/95	7/6
		TEL+HCTZ	80/25	352	148/95	10¶/7¶(TEL 80+HCTZ 12.5)
AZILSARTAN (AZL)/CHLORTHALIDONE (CHL) versus component monotherapy						
Sica et al 2012 (71)	8	AZL+CHL	20+12.5	156	165/95	34¶/14¶ (vs both AZL 25 and CHL 12.5)
		AZL+ CHL	20+25	154	165/96	37¶/16¶ (vs both AZL 20 and CHL 25)
		AZL+ CHL	40+12.5	147	165/96	37¶/16¶ (vs both AZL 40 and CHL 12.5)
		AZL+ CHL	40+25	156	164/94	40¶/17¶ (vs both AZL 40 and CHL 25)
		AZL+ CHL	80+12.5	153	165/94	37¶/17¶ (vs both AZL 80 and CHL 12.5)
		AZL+ CHL	80+25	162	164/94	40¶/19¶ (vs both AZL 80 and CHL 25)
		AZL	20	155	163/95	20/7
		AZL	40	153	164/95	23/9
		AZL	80	162	164/95	24/10
		CHL	12.5	157	164/96	21/7
		CHL	25	159	166/96	27/9

¶statistically significant versus the equivalent component monotherapy

€forced titration

*24 hour ambulatory blood pressure monitoring data and the rest are clinic blood pressure data

CAN – Candesartan. EPR – Eprosartan. OLM – Olmesartan. LOS – Losartan. IRB – Irbesartan. VAL – Valsartan. TEL – Telmisartan. AZL – Azilsartan. HCTZ – Hydrochlorothiazide. CHL – Chlorthalidone

Table 5

Blood Pressure Reductions in Randomized Controlled Trials of Angiotensin Receptor Antagonists and Amlodipine in Combination versus Component Monotherapy

Study and Year	Duration (weeks)	Drug	Dosage (mg)	Sample size (n)	Mean baseline blood pressure (mmHg)	Mean BP reductions from baseline (mmHg)
OLMESARTAN (OLM)/AMLODIPINE (AML) versus component therapy						
Chrysant et al 2008 (72)	8	OLM+AML	10+5	163	166/102	24[¶]/14[¶] (vs both AML 5 and OLM 10)
		OLM+AML	10+10	162	163/101	25[¶]/16[¶] (vs both AML 10 and OLM 10)
		OLM+AML	20+5	161	164/102	24[¶]/14[¶] (vs both AML 5 and OLM 20)
		OLM+AML	20+10	160	164/101	29[¶]/17[¶] (vs both AML 10 and OLM 20)
		OLM+AML	40+5	162	162/101	25[¶]/16[¶] (vs both AML 5 and OLM 40)
		OLM+AML	40+10	162	166/102	30[¶]/19[¶] (vs both AML 10 and OLM 40)
		OLM	10	161	163/102	12/8
		OLM	20	161	164/102	14/9
		OLM	40	162	163/101	16/10
		AML	5	161	163/102	15/9
		AML	10	163	164/102	20/13
VALSARTAN (VAL)/AMLODIPINE (AML) versus component therapy						
Philipp et al 2007 *Study Group 1* (73)	8	VAL+AML	40+5	125	153/99	20[¶]/15[¶] (vs both AML 5 and VAL 40)
		VAL+AML	80+5	128	153/99	21[¶]/15[¶] (vs both AML 5 and VAL 80)
		VAL+AML	160+5	127	153/99	20[¶]/14[¶] (vs both AML 5 and VAL 160)
		VAL+AML	320+5	127	153/99	23[¶]/16[¶] (vs both AML 5 and VAL 320)
		VAL+AML	40+2.5	129	153/100	16[¶]/11 (vs both AML 2.5 and VAL 40)
		VAL+AML	80+2.5	130	152/100	17[¶]/13[¶] (vs both AML 2.5 and VAL 80)
		VAL+AML	160+2.5	127	152/99	17[¶]/13[¶] (vs both AML 2.5 and VAL 160)[§]
		VAL+AML	320+2.5	129	152/99	18[¶]/14[¶] (vs AML 2.5 only)
		VAL	40	127	154/99	12/10
		VAL	80	124	153/99	13/10

Study and Year	Duration (weeks)	Drug	Dosage (mg)	Sample size (n)	Mean baseline blood pressure (mmHg)	Mean BP reductions from baseline (mmHg)
		VAL	160	128	152/99	15/11
		VAL	320	128	155/99	16/13
		AML	2.5	126	154/100	12/9
		AML	5	128	153/99	15/12
Philipp et al 2007 *Study Group 2*(73)	8	VAL+AML	160+10	209	157/99	28¶/18¶ (vs both AML 10 and VAL 160)
		VAL+AML	320+10	210	157/99	28¶/19¶ (vs both AML 10 and VAL 320)
		VAL	160	207	156/99	20/13
		VAL	320	208	158/99	2013
		AML	10	207	156/99	24/16
Flack et al 2009 (FLACK) €Ω(74)	8	VAL+AML	160/320+5/10	286	170/99	33¶/14¶ (vs AML 10 only)
		AML	5/10	286	171/98	27/11
TELMISARTAN (TEL)/AMLODIPINE (AML) versus component therapy						
Neutel et al 2012 (75)	8	TEL+AML	80/10	421	185/103	48¶/19¶ (vs both AML 10 and TEL 80)
		TEL	80	217	186/103	37/14
		AML	10	220	185/103	43/16
LOSARTAN (LOS)/AMLODIPINE (AML) versus component therapy						
Hong et al 2012 (76)δ	8	LOS+AML	100+5	70	142/98	13¶/12¶ (vs LOS 100)
		LOS	100	72	141/97	3/3
CANDESARTAN (CAN)/AMLODIPINE (AML) versus component therapy						
Rakugi et al 2012 (77)	12	CAN+AML	8+5	101	152/95	27¶/16¶ (vs both AML 5 and CAN 8)
		CAN+AML	8+2.5	36	152/96	20/12
		CAN+AML	4+5	36	155/97	27/17
		CAN+AML	4+2.5	35	153/96	16/10
		CAN	8	100	155/97	14/8
		AML	5	100	153/96	20/11

¶ statistically significant versus component monotherapy

€ Forced titration

ΩAfrican-American patients

δKorean patients

$\S$statistically significant for SBP reduction versus AML monotherapy alone and DBP reduction for both component monotherapies

CAN – Candesartan. EPR – Eprosartan. OLM – Olmesartan. LOS – Losartan. IRB – Irbesartan. VAL – Valsartan. TEL – Telmisartan. AZL – Azilsartan. AML - Amlodipine

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Table 6

Blood Pressure Reductions in Randomized Controlled Trials of Angiotensin Receptor Antagonists with Diuretic and Amlodipine Triple Combinations versus Dual Therapy

Study and Year	Duration (weeks)	Drug	Dosage (mg)	Sample size (n)	Mean baseline blood pressure (mmHg)	Mean BP reductions from baseline (mmHg)
Calhoun et al 2009 (80) €	8	VAL+HCTZ+AML	160+12.5+5/320 +25+10	571	170/106	40[¶]/25[¶] (versus all dual therapies)
		VAL+HCTZ	160+12.5/320+25	553	170/106	32/20
		VAL+AML	160+5/320+10	558	170/107	34/22
		HCTZ+AML	12.5+5/25+10	554	171/107	32/20
Oparil et al 2010 (81)	12	OLM+HCTZ+AML	40+25+10	614	168/101	37[¶]/22[¶] (versus all dual therapies)
		OLM+HCTZ	40+25	627	169/101	30/17
		OLM+AML	40+10	624	168/101	30/18
		HCTZ+AML	25+10	593	169/101	28/15

[¶]statistically significant versus dual therapy

€Forced titration

VAL – Valsartan. AML – Amlodipine. HCTZ – Hydrochlorothiazide

Table 7

The Impact of Angiotensin Receptor Blocker Therapies on Cardiovascular Outcomes

Study and Year	ARB (n)	Comparator (n)	Primary Outcome	Main Results	Comments
Hypertension primary outcome trials					
LIFE 2001 (89)	Losartan 100 mg/day (4,605)	Atenolol (4,588)	Death, myocardial infarction, or stroke	Losartan reduced cardiovascular morbidity and death more than atenolol (RR 0.87, p=0.021)	Similar reduction in BP achieved between two groups with left ventricular hypertrophy
VALUE 2003 (90)	Valsartan 160 mg/day (7,649)	Amlodipine 10mg/day (7,596)	Cardiovascular mortality and morbidity	No difference between valsartan and amlodipine (HR 1.04, p=0.49)	Amlodipine treatment resulted in greater BP reduction compared to valsartan causing potential confounding in high risk patients
SCOPE 2003 (91)	Candesartan 16 mg/day (2477)	Placebo * (2460)	Cardiovascular death, non-fatal stroke and non-fatal myocardial infarction	No difference between candesartan and placebo (p=0.19).	Candesartan reduced non-fatal stroke by 27.8% (p=0.04)
Renal Disease					
ONTARGET (86)	Telmisartan 80 mg/day (8,541)	Telmisartan/ramipril combination 80/10 mg/day (8,502) Ramipril 10 mg/day (8.576)	Composite of dialysis, doubling of serum creatinine, and death	Composite primary renal outcome was similar between telmisartan (HR 1.00, 95% CI 0.92–1.09), but increased with combination therapy (HR 1.09, 1.01–1.18; p=0.037)	Patients were aged 55 years or older with established atherosclerotic vascular disease or with diabetes with end-organ damage.
IRMA-2 2001 (93)	Irbesartan 150 mg/day (195)/ Irbesartan 300 mg/day (194)	Placebo * (201)	Progression to diabetic nephropathy based	Reduction of progression to diabetic	The effect of irbesartan was independent of

Study and Year	ARB (n)	Comparator (n)	Primary Outcome	Main Results	Comments
			on increases in proteinuria on increases in proteinuria	nephropathy IRB 300mg HR 0.30, p< 0.001; IRB 150mg HR 0.61 p=0.08)	its antihypertensive effect
RENAAL 2001 (95)	Losartan 100 mg/day (751)	Placebo* (762)	Doubling of the baseline serum creatinine, development of end-stage renal disease, or death from any cause	Losartan reduced the incidence of doubling of serum creatinine (25% risk reduction, p=0.006) and incidence of end-stage renal disease (ESRD) (28% risk reduction, p=0.002) versus placebo	Losartan showed no ESRD mortality benefit
IDNT 2001 (96)	Irbesartan 300 mg/day (579)	Amlodipine 10 mg/day (567) Placebo* (569)	Doubling of the serum creatinine, development of ESRD, or death from any cause.	Irbesartan reduced the incidence of doubling of serum creatinine versus amlodipine (37% risk reduction, p<0.001) and placebo (33% risk reduction, p=0.003)	Irbesartan was associated with 23% lower incidence of ESRD versus placebo and amlodipine (both p=0.07).
Heart Failure					

Study and Year	ARB (n)	Comparator (n)	Primary Outcome	Main Results	Comments
ELITE II 2000 (97)	Losartan 50 mg/day (1,578)	Captopril 150 mg/day (1,574)	All cause mortality, and sudden death or resuscitated arrest	No significant differences in all-cause mortality with average annual mortality of 11.7% in the losartan arm versus 10.4% in the captopril arm (HR 1.13, p= 0.16)	Losartan was better tolerated than captopril
CHARM-Alternative 2003 (101)	Candesartan 32 mg/day (1,013)	Placebo (1,015)	Composite of cardiovascular death or hospital admission for CHF	Candesartan reduced cardiovascular death and hospitalization for CHF versus placebo (adjusted HR 0.70, p<0.0001)	ACE inhibitor intolerant patients
CHARM-Added 2003 (102)	Candesartan 32 mg/day (1,276)	Placebo^ (1,272)	Composite of cardiovascular death or hospital admission for CHF	Candesartan reduced cardiovascular death and hospitalization for CHF versus placebo (unadjusted HR 0.85, p=0.011).	Patients were on background of lisinopril, enalapril, captopril or ramipril: ARB +ACE inhibitor had higher withdrawal rate due to prespecified doubling of creatinine and hyperkalemia
CHARM-Preserved 2003 (103)	Candesartan 32 mg/day (1,514)	Placebo (1,509)	Composite of cardiovascular death or hospital admission for CHF	Trend towards reduction in cardiovascular mortality and morbidity versus placebo but not statistically significant (adjusted HR 0.86, p=0.051).	

Study and Year	ARB (n)	Comparator (n)	Primary Outcome	Main Results	Comments
ValHeFT 2001 (104)	Valsartan 320 mg/day (2,511)	Placebo^ (2,499)	Combined end point of mortality and morbidity	Valsartan reduced mortality and morbidity versus placebo (RR 0.87, P=0.009)	Valsartan was associated with improvement in NYHA class, LVEF and quality of life versus placebo.
I-PRESERVE 2008 (105)	Irbesartan 300mg/day (2,061)	Placebo (2,067)	Composite of death from any cause or hospitalization for a cardiovascular cause (heart failure, myocardial infarction, unstable angina, arrhythmia, or stroke)	No difference between the two groups. (HR Irbesartan vs placebo, 0.95; p=0.35)	Patients with preserved LV function
Post-Myocardial Infarction					
VALIANT 2003 (98)	Valsartan 320mg/day (4,909)	Captopril 150mg/day (4, 909) / Valsartan 160mg/day+Captopril 150mg/day (4, 885)	All-cause mortality	No difference between three groups (HR VAL vs captopril, 1.00, p=0.98; HR VAL +captopril vs captopril 0.98, p=0.73)	Higher adverse effects with combined therapy
OPTIMAAL 2002 (99)	Losartan 50mg/day (2,744)	Captopril 150mg/day (2,733)	All-cause mortality	No difference between valsartan and captopril (RR 1.13 [95% p=0.07).	Losartan was more tolerated than captopril
Stroke Prevention					
LIFE 2001 (89)	Losartan 100 mg/day (4,605)	Atenolol (4,588)	Nonfatal and fatal stroke	Favored losartan over atenolol showing a 24.9% relative risk reduction compared with atenolol (p=0.001).	Similar reduction in BP achieved between two groups with left ventricular hypertrophy
PRoFESS (130)	Telmisartan 80mg/day (10,146)	Placebo	Recurrent Stroke	No difference between telmisartan	

Study and Year	ARB (n)	Comparator (n)	Primary Outcome	Main Results	Comments
					and placebo. (HR 0.95, p=0.023).
					and placebo. (HR 0.95, p=0.023).
					and placebo. (HR 0.95, p=0.023).

LIFE Losartan Intervention for Endpoint Reduction in Hypertension. SCOPE Study on Cognition and Prognosis in the Elderly. VALUE Valsartan Antihypertensive Long-term Use Evaluation. RENAAL Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan. IDNT Irbesartan Diabetic Nephropathy Trial. MARVAL Microalbuminuria Reduction With Valsartan in Patients With Type 2 Diabetes Mellitus. IRMA 2 Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria. ELITE II Losartan Heart Failure Survival Study. VALHEFT Valsartan Heart Failure Trial. CHARM Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity). I-PRESERVE Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction. VALIANT Valsartan in Acute Myocardial Infarction. OPTIMAAL (Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan). PRoFESS Prevention Regimen for Effectively Avoid Second Strokes. ONTARGET Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk.

*
Other antihypertensive medications allowed;

^
Patients allowed to use ACE inhibitors and beta blockers