

The Management of Hypertension:

Focus on Olmesartan
Medoxomil and
The Angiotensin II
Receptor Blockers
(ARBs)

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Goals

- To educate and inform pharmacists about the use of angiotensin II receptor antagonists (ARBs) in the treatment of hypertension.
- To provide an overview of the newest member of the ARB class, olmesartan medoxomil.

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Objectives

- Discuss the epidemiology of hypertension in the U.S., and the cardiovascular risks associated with elevated diastolic and systolic blood pressure.
- Describe the non-pharmacological and pharmacological approaches to the treatment of hypertension.
- Review the role of the renin-angiotensin-aldosterone system in blood pressure homeostasis.
- Describe the mechanism of action of the ARBs.
- Identify the advantages and disadvantages of the ARBs compared to other antihypertensive agents.
- Discuss and compare the pharmacokinetics, efficacy, and safety of ARBs.
- Discuss the clinical pharmacology, pharmacokinetics, and efficacy and safety data for olmesartan medoxomil.
- Discuss pending and completed clinical outcomes trials performed with the ARBs.

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The Management of Hypertension: Focus on Olmesartan Medoxomil and The Angiotensin II Receptor Blockers (ARBs)

Introduction

Approximately 50 million Americans suffer from hypertension.¹ The blood pressure of hypertensive patients should be adequately controlled to decrease the incidence of complications. Sometimes blood pressure control can be achieved non-pharmacologically, however, therapy with antihypertensive drugs is often required. Although there are several classes of antihypertensive medications, the treatment of hypertension remains a challenge as the blood pressure of many patients remains uncontrolled. The angiotensin II receptor blockers (ARBs) are the newest addition to the antihypertensive drug market. Since the ARBs have a better overall safety and tolerability profile than other available antihypertensive therapies, and boast a convenient once-daily dosing schedule, patients may be more likely to comply with therapy and reach their blood pressure goals. The completion of ongoing studies with ARBs will investigate the effects of these drugs on cardiovascular morbidity and mortality. The focus of a portion of this monograph will be on the newest ARB, olmesartan medoxomil, and its characteristics, safety, efficacy, and comparative efficacy with other selected antihypertensive agents.

Hypertension in the US

Hypertension continues to remain a significant risk factor that pharmacists encounter daily in their practice. According to the 2001 Current Medical Diagnosis and Treatment, 50 million Americans have elevated blood pressure (systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg). Of these, 68% are aware of their diagnosis, 53% are receiving treatment, and only 27% of hypertensive patients in the US have their blood pressure under control.¹ These results indicate that the management of hypertension remains an enormous challenge for health care providers. One possible reason for the alarmingly low percentage of patients at goal may include noncompliance with therapy due to either adverse reactions related to the medication or an inconvenient antihypertensive medication dosing schedule. Pharmacists may assist patients in reaching their goal blood pressure by educating them on the potentially serious adverse outcomes associated with noncompliance, and ensuring that patients are on the most appropriate agents based on their adverse effect and drug interaction profiles, potential disease interactions, dosing frequency, route, and cost.

Hypertension is classified as either primary or secondary. Primary hypertension, also known as essential hypertension, accounts for 95% of diagnosed hypertensive patients. Primary hypertension has an unknown etiology.² Secondary hypertension results from another medical condition, such as Cushing's syndrome, primary hyperaldosteronism, pregnancy, renal disease, estrogen use, chronic alcohol abuse, or the use of certain medications such as NSAIDs or cyclosporin.³

Regardless of the type of hypertension, major devastating and fatal complications are associated with elevated blood pressure. Complications include, but are not limited to: cardiovascular disease, cerebrovascular disease, renal disease, retinopathy, and atherosclerosis.³

The goal of antihypertensive therapy is to decrease the morbidity and mortality risk associated with high blood pressure. Numerous clinical trials have shown that pharmacological treatment of hypertension is associated with significant decreases in the incidence of developing these complications. For example, a meta-analysis published by MacMahon et al reported antihypertensive therapy resulted in a 36% risk reduction in cerebrovascular disease and a 10% risk reduction in coronary heart disease incidence.² (Figure 1)

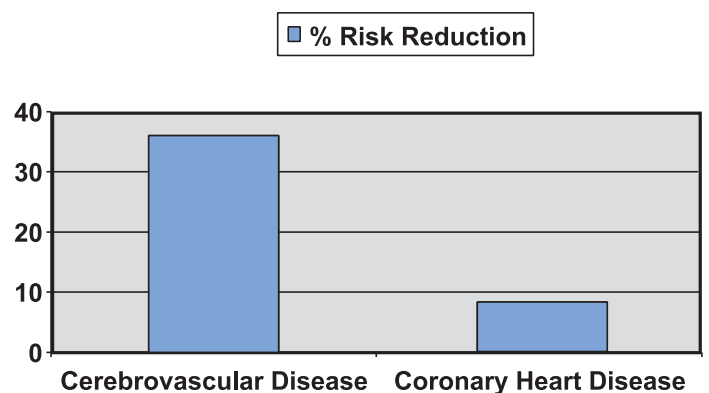


Figure 1: THE EFFECT OF ANTIHYPERTENSIVE DRUG THERAPY ON RISK REDUCTION²

The Treatment of Hypertension— Nonpharmacological Approaches:

Lifestyle modifications should be the first step employed for the treatment of all hypertensive patients. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI) recommends that patients maintain a healthy body weight, exercise regularly, stop smoking, and limit alcohol consumption.⁴ Additionally, patients should eat a well-balanced diet, reduce intake of dietary saturated fats, cholesterol, and sodium, and maintain adequate potassium, calcium, and magnesium intake. In some people, however, even strict adherence to these lifestyle modifications will not be sufficient to control their hypertension. For these people, drug treatment is indicated while continuing to adhere to lifestyle modification.¹

The Treatment of Hypertension— Pharmacological Approaches:

Pharmacotherapy is often necessary to control hypertension. There are numerous classes of medications with different mechanisms of action that are used in the treatment of hypertension. New antihypertensive classes, as well as additional agents within the classes, continue to be developed to increase efficacy, compliance, and control rates of hypertensive patients. The JNC-VI reports that optimal drug formulations should provide 24-hour efficacy with a once-daily dose. Ideally, this long-acting formulation would increase compliance and result in smooth, persistent blood pressure lowering.⁴

Diuretics, developed in the early 1950s, were the first antihypertensive agents introduced into the market. Since the introduction of diuretics, eight other antihypertensive classes have been developed. The nine classes of antihypertensives, in order of development, include: diuretics, alpha blockers, direct vasodilators, central adrenergic inhibitors, peripheral adrenergic inhibitors, beta-blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, and ARBs.² This monograph will focus on the newest addition to the antihypertensive armamentarium, the ARBs.

The selection of pharmacological agents should be done on an individual basis. Some factors influencing the choice of agents include patients' demographic features, concomitant disease states, and plasma renin levels.⁴ Clinical studies

report that specific drug classes can provide additional benefits beyond blood pressure lowering in certain disease states. In light of these trials, JNC-VI recommends the use of ACE inhibitors for treatment of hypertensive patients with concomitant diabetes or heart failure. (Table 1) However, if these patients cannot tolerate an ACE inhibitor, JNC-VI recommends that an ARB may be substituted. On the other hand, certain drug classes can have a negative effect on specific disease states and patient populations. For example, beta-blockers should be avoided in asthmatics and diabetics, while ACE inhibitors and ARBs should be avoided in pregnant patients.

Table 1: COMPELLING INDICATIONS FOR ANTIHYPERTENSIVE AGENTS UNLESS CONTRAINDICATED⁴

Indication	Drug Therapy
Diabetes mellitus (type 1) with proteinuria	ACE inhibitors
Heart failure	ACE inhibitors, diuretics*
Isolated systolic hypertension	Diuretics (preferred), Calcium antagonists (long-acting DHP*)
Myocardial infarction	Beta-blockers (non-ISA), ACE inhibitors (with systolic dysfunction)

*Since JNC-VI, beta-blockers have become standard treatment for heart failure.

**DHP = dihydropyridine calcium antagonists.

The Role of Renin-Angiotensin-Aldosterone System (RAAS) in Blood Pressure Homeostasis

ARBs and ACE inhibitors work by targeting the RAAS. The RAAS is an important regulator of blood pressure homeostasis. Any one of the following triggers can activate RAAS: a low blood pressure, a decrease in renal blood flow, and/or a low level of serum sodium. Once RAAS is activated, the first step in the pathway is release of renin from the juxtaglomerular complex of the nephron, which converts angiotensinogen into angiotensin I. Next, either ACE or a nonspecific chymase generates angiotensin II from angiotensin I. One function of angiotensin II is to increase blood pressure by three distinct mechanisms: angiotensin II 1) increases peripheral vascular resistance; 2) stimulates release of aldosterone from the adrenal medulla, which induces sodium and water retention; and 3) causes smooth muscle cell proliferation and hypertrophy, further enhancing vascular tone.⁵

There are several key differences between the ARBs and ACE inhibitors. The ACE inhibitors work early in the RAAS cascade by blocking ACE, which aids in decreasing the pro-

duction of angiotensin II. (Figure 2) In addition, ACE inhibitors prevent the breakdown of bradykinin, prostacyclin, and endothelium-derived relaxing factor. The accumulation of these products is thought to be responsible for potential troublesome adverse effects that may be experienced with ACE inhibitor therapy, such as cough and angioedema.⁶ However, inhibiting the ACE enzyme does not completely inhibit RAAS, since angiotensin II can be generated by other non-ACE pathways. By contrast, the ARBs block the angiotensin II subtype 1 (AT₁) receptor. This selective blockade antagonizes the effects of angiotensin II at the target site, regardless of the pathway through which it was formed. (Figure 2) Blockage of the AT₁ receptor promotes vasodilation by relaxing vascular smooth muscle. ARBs also increase renal salt and water excretion, reduce plasma volume, and are believed to decrease cellular hypertrophy. In addition, because ARBs do not cause increases in bradykinin levels, ARBs generally have a more favorable side effect profile when compared to ACE inhibitors.⁶

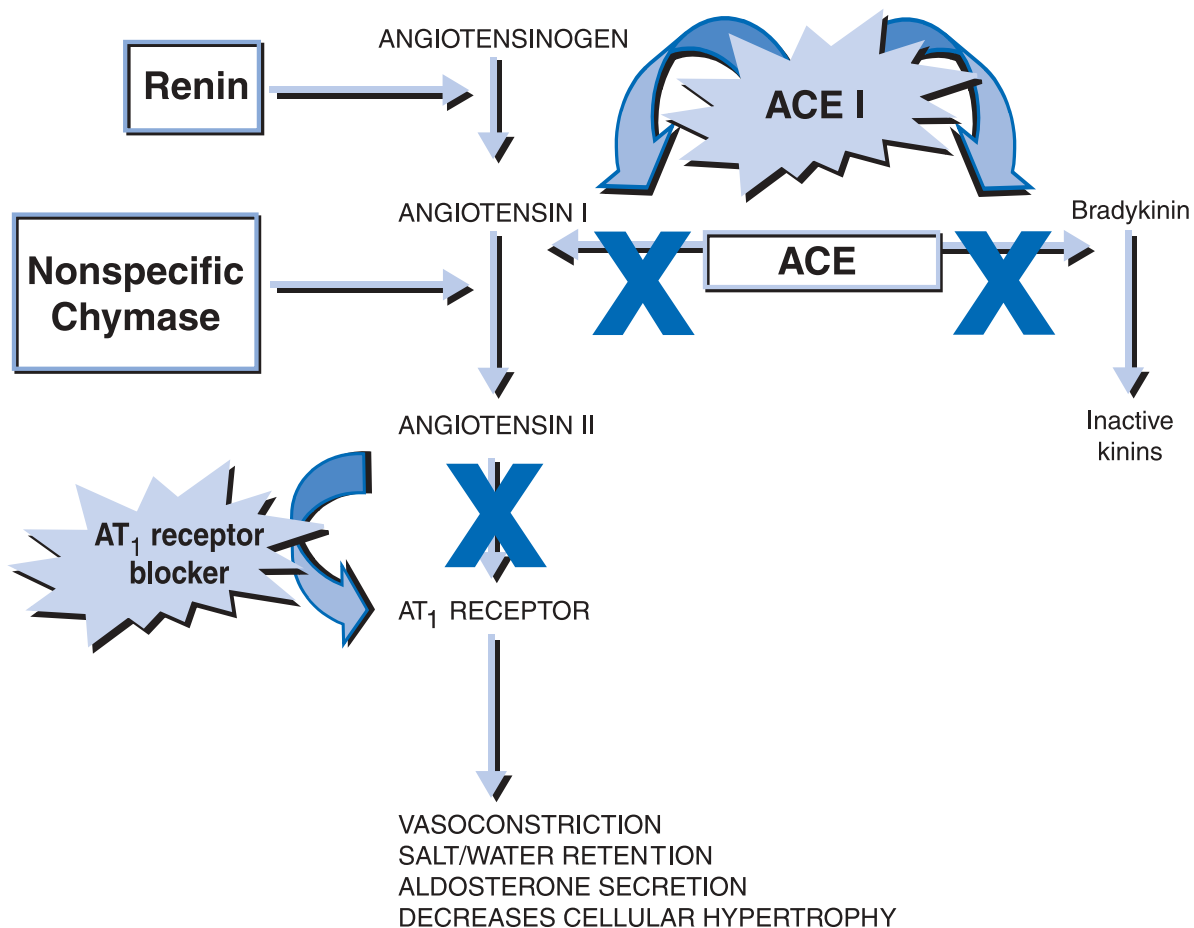


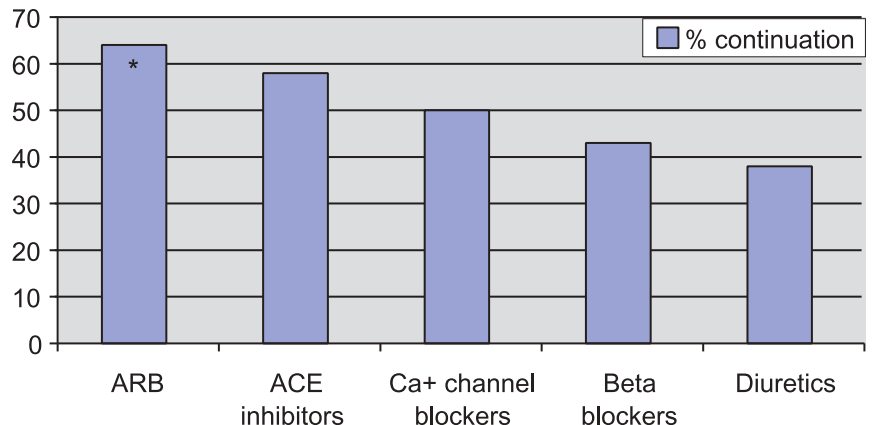
Figure 2: RENIN ANGIOTENSIN ALDOSTERONE SYSTEM¹

Advantages and Disadvantages of the ARBs

The ARB class has been shown to have similar blood pressure lowering effects compared to the older antihypertensive agents. However, the major advantages of the ARB class over alternative current antihypertensive therapies include an improved overall safety and tolerability profile that has been shown to be similar to placebo and a convenient once-daily dosing schedule. These two features of the ARB class may improve patient adherence to these antihypertensive agents. Bloom and colleagues evaluated the 1-year compliance rate for ACE inhibitors, diuretics, calcium channel blockers, and angiotensin II receptor blockers in a recently published study of 21,723 patients.² Compliance was measured based on prescription refill rates. The results of this study showed that the percentage of patients that continued initial therapy on the ARB losartan was significantly higher than with the other antihypertensive therapies. (Figure 3)

First-dose hypotension seldomly occurs with ARBs. In addition, ARBs do not change resting heart rate, and rebound hypertension does not occur after these agents are discontinued. Metabolically, ARBs have an excellent profile. These agents have neutral effect on lipids and glucose tolerance, which may be advantageous in treatment of hypertensive patients with concomitant diabetes or hyperlipidemia.

It is important to be aware that drugs that act directly on the RAAS can cause fetal and neonatal morbidity and death when administered to pregnant women. The use of these drugs during the second and third trimesters of pregnancy has been associated with fetal/neonatal injury. Therefore, ACE inhibitors and ARBs are contraindicated in pregnancy and, if pregnancy is detected, these agents should be discontinued.



* $P < 0.05$ for ARB vs ACE inhibitors

Figure 3: CONTINUATION OF INITIALLY PRESCRIBED ANTIHYPERTENSIVE AGENT AT 12 MONTHS⁸

Clinical Outcome Studies With ARBs

The main objective for treating hypertension is to reduce risk of morbidity and mortality associated with cardiovascular disease. Since ARBs are the newest class of antihypertensive medication, there is limited outcome data available for these agents. Several studies have examined the potential clinical benefits of ARBs on mortality trends in patients with cardiac failure (ie, ELITE I¹ [Evaluation of Losartan In The Elderly], ELITE II³ [Evaluation of Losartan In The Elderly round II], Val-HeFT² [Valsartan Heart Failure Trial], and LIFE¹⁵ [Losartan Intervention For Endpoint]). Other outcome trials have evaluated the use of ARBs in patients with type 2 diabetes (ie, RENAAL⁴ [Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan], IDNT⁵ [Irbesartan in patients with Nephropathy Due to Type 2 Diabetes], and IRMA II⁶ [Irbesartan in patients with type 2 diabetes and MicroAlbuminuria]). Brief summaries of these studies follow.

ELITE I⁹ was the first trial that compared ARBs versus ACE inhibitors in the treatment of congestive heart failure (HF). This was a multi-center, randomized, double-blind, active comparator, controlled study of 722 patients aged 65 or older with HF. Patients were titrated to losartan 50 mg QD or captopril 50 mg TID for 48 weeks. The primary endpoint of the trial, persistent increase in creatinine, was the same in both groups (10.5%, $P=0.63$) This study detected a trend for decreased mortality incidence in HF patients treated with losartan when compared to patients treated with captopril. The secondary endpoint of death and/or hospitalization for heart failure was observed in 9.4% of the losartan and 13.2% of the captopril patients ($P=0.075$). In addition, fewer losartan patients discontinued therapy due to an adverse event (12% versus 21% for captopril, $P=0.002$).⁹

ELITE II¹⁰ was designed to validate the results that were reported in ELITE I⁹. ELITE II, unlike ELITE I, had a large sample size of 3152 patients and was properly powered to detect a mortality benefit in losartan-treated patients. ELITE II was a randomized, double-blind, controlled trial of HF patients aged 60 years or older. ELITE II incorporated the same study design as ELITE I. The effect of losartan on all-cause mortality was not found to be superior to captopril in this study. The results revealed lower rates of all-cause morbidity and mortality and of sudden death in patients given captopril, although the differences did not reach statistical significance. However, in terms of tolerability, the results of ELITE II mimicked ELITE I. Both trials showed losartan to be significantly better tolerated than captopril. In ELITE II 14.5% of patients receiving captopril withdrew due to adverse effects, compared to a 9.5% withdrawal rate in losartan-treated patients ($P<0.001$).¹⁰

Val-HeFT¹¹ was a randomized, placebo-controlled, double-blind, parallel-group trial of 5010 patients with HF. This study evaluated the effects of the addition of the ARB valsartan 160 mg BID to standard therapy for HF. The results from this trial indicated that valsartan significantly reduced the combined primary endpoint of morbidity and mortality by 13% when compared to placebo ($P=0.009$). In addition, treatment with valsartan reduced first hospitalization rate for HF by 27% ($P<0.001$).¹¹

LIFE¹⁵ was a multicenter, double-blind, prospective, randomized, controlled study with 2 parallel groups. This study investigated the long-term (2-4 years) effect of losartan versus atenolol on reduction of morbidity and mortality in hypertensive patients with documented left ventricular hypertrophy (LVH). This study enrolled 9222 patients between 55 and 80 years of age with hypertension and documented LVH. The primary composite endpoint was defined as death from MI, stroke, or HF. Patients received once-daily atenolol-based or losartan-based antihypertensive therapy for at least four years and until 1040 patients had a primary cardiovascular event. Losartan-based therapy was associated with less cardiovascular morbidity and mortality, less stroke, less onset of diabetes, and better tolerability with significantly fewer discontinuations for adverse events for similar blood pressure reduction when compared to atenolol.

The therapeutic benefit of ARBs in patients with type 2 diabetes mellitus was examined in RENAAL¹², IDNT¹³, and IRMA II¹⁴. RENAAL and IDNT evaluated the effect of ARBs on the progression of diabetes, while IRMA II examined whether ARBs reduce proteinuria in type 2 diabetic patients. These studies are described below.

RENAAL¹² was a multicenter, double-blind, randomized, placebo-controlled study designed to evaluate the renal protective effects of losartan in 1513 patients with type 2 diabetes mellitus and nephropathy. Patients were randomized to receive losartan 50 mg titrated to 100 mg QD, or placebo. The primary endpoint

for RENAAL was the composite of a doubling of the baseline serum creatinine concentration, end-stage renal disease, or death. Losartan resulted in a significant risk reduction of 16% ($P=0.02$) in the primary composite endpoint. Losartan also dramatically reduced the risk of first hospitalization for heart failure by 32% ($P=0.005$) and decreased the level of proteinuria by 35% ($P<0.001$) compared to placebo.¹²

IDNT¹³ was a multicenter, double-blind, prospective, randomized study of 1715 hypertensive patients with nephropathy related to type 2 diabetes. IDNT was conducted to determine whether the use of an ARB or a calcium channel blocker would provide protection against the progression of nephropathy related to type 2 diabetes mellitus. Patients were randomized to receive irbesartan 300 mg QD, amlodipine 10 mg QD, or placebo. The primary composite endpoint was a doubling of baseline serum creatinine concentration, the development of end-stage renal disease, or death from any cause. Although blood pressure control was similar in all groups, the incidence of the primary composite endpoint was significantly lower in the irbesartan cohort compared with either the amlodipine or placebo groups. In terms of the primary composite endpoint, irbesartan therapy was associated with a 20% relative risk reduction versus placebo-treated patients ($P=0.02$), and a 23% ($P=0.006$) relative risk reduction versus the amlodipine-treated patients.¹³

IRMA II¹⁴ was a multinational, double-blind, randomized, placebo-controlled study designed to evaluate the renoprotective effects of an ARB in 590 hypertensive patients with type 2 diabetes and microalbuminuria. Patients were randomized to irbesartan 150 mg QD, irbesartan 300 mg QD, or placebo. The primary outcome was the time to the onset of diabetic nephropathy. The primary endpoint was reached in 5.2% of the irbesartan 150 mg QD group, 9.7% of the irbesartan 300 mg group, and 14.9% of the placebo group ($P<0.001$). The level of urinary albumin excretion was reduced by 24% in the irbesartan 150 mg cohort, 38% by the irbesartan 300 mg group, and 2% in the placebo group ($P<0.001$).¹⁴

Other clinical trials are currently under way to determine if ARBs may reduce cardiovascular morbidity and mortality rates in different groups of hypertensive patients. (Table 3) SCOPE⁷ (Study on Cognition and Prognosis in the Elderly), VALUE⁸ (The Valsartan Antihypertensive Long-term Use Evaluation), and VALIANT⁹ (Valsartan in Acute Myocardial Infarction Trial) are all designed to determine if ARB usage affects mortality in hypertensive patients. These clinical studies, evaluating different ARBs in various cardiovascular disease settings, will further aid in defining the role of this class of agents in the treatment of hypertension and associated complications.

Table 2: COMPLETED CLINICAL TRIALS WITH ARBs

Trial	Number of Patients	Patients	Treatment	Primary End Point	Results
RENAAL ¹²	1,513	Type 2 DM with albuminuria	Losartan vs placebo	Time to doubling of serum creatinine, ESRD, or death	16% reduction in combined endpoint (2xCr; ESRD; death) and 32% reduction in hospitalizations ($P=0.02$)
IDNT ¹³	1,715	HTN and type 2 diabetic nephropathy	Irbesartan, amlodipine, placebo	Time to doubling of serum creatinine, ESRD, or death	20% RR in 2xCr; ESRD; death compared to placebo ($P=0.02$) and 23% RR compared to amlodipine ($P=0.006$)
IRMA II ¹⁴	590	HTN with type 2 DM	Losartan vs placebo	Time to onset of diabetic nephropathy	Albumin excretion decreased by 24% and 38% ($P<0.001$) and nephropathy incidence decreased by 10% and 5% ($P<0.001$), respectively (150 and 300 mg irbesartan)
ELITE ¹⁹	722	>65 y/o with HF	Losartan vs captopril	All-cause mortality	Lower mortality with losartan than captopril
ELITE II ¹⁰	3,152	>65 y/o with symptomatic HF	Losartan vs captopril	All-cause mortality	Trend for captopril over losartan in the reduction of all-cause mortality. Significantly lower discontinuation with losartan
Val-HeFT ¹¹	5,010	CHF	Valsartan vs placebo	All-cause mortality and cardiac morbidity	Reduction in all-cause mortality and morbidity 13% ($P=0.009$) and HF hospitalizations ($P<0.001$) reduced by 27%
LIFE ¹⁵	9,194	HTN and LVH	Losartan vs atenolol	Cardiovascular mortality and morbidity	Reduction in composite endpoint (CV mortality, stroke, and MI) 13% ($p=0.021$) with losartan, 25% reduction ($p<0.001$) in new-onset diabetes with losartan

Table 3: ONGOING CLINICAL TRIALS WITH ARBs

Trial	Number of Patients	Patients	Treatment	Primary End Point	Expected Date of Completion
SCOPE ¹⁶	4,000	70-89 y/o and DBP 90-99 mm Hg	Candesartan vs placebo	Cardiovascular mortality and morbidity	2002
VALUE ¹⁷	14,000	HTN	Valsartan vs amlodipine	Cardiovascular mortality and morbidity	2004
VALIANT ¹⁸	14,500	Post-MI with HF ± LV dysfunction	Valsartan alone, captopril alone, valsartan + captopril	All-cause mortality	2005

Pharmacokinetics of Current ARBs

The FDA has approved the following 6 ARBs for the treatment of hypertension: losartan potassium, valsartan, irbesartan, eprosartan, candesartan cilexetil, and telmisartan. Although all of the ARBs have similar core structures, these agents exhibit differences in their binding affinity for the AT₁ receptor. Binding to the AT₁ receptor is characterized as either insurmountable binding or surmountable binding. Insurmountable antagonism indicates suppression of the agonist response despite escalations in agonist concentration. On the other hand, surmountable antagonism implies that antagonist blockade can eventually be overcome if high enough agonist concentration is present.¹ Irbesartan, candesartan cilexetil, and telmisartan are insurmountable antagonists, whereas losartan (parent compound), valsartan, and eprosartan are surmountable antagonists.^{2,3} These differences in binding may account for changes in both the pharmacokinetic and pharmacodynamic profiles of these agents.²²

The pharmacokinetics of the currently approved ARBs are listed in Table 4. All of the ARBs exhibit distinctive pharma-

cokinetic profiles.²¹ Two ARBs, losartan potassium and candesartan cilexetil, are prodrugs. Candesartan cilexetil is activated in the small intestine, while losartan potassium, the oldest ARB agent, is biotransformed in the liver by the cytochrome P450 (CYP 450) enzymes. Medications, which inhibit the CYP 450 enzymes, may interfere with the conversion of losartan to its metabolite, possibly decreasing its effectiveness. Clinically significant drug interactions between losartan potassium with rifampin and fluconazole have been reported. Rifampin induces the metabolism of losartan, and fluconazole decreases the metabolism of losartan potassium.^{22,23} The ARBs also vary tremendously in their bioavailabilities and half-lives. Bioavailability ranges from 13% for eprosartan to 80% for irbesartan. Losartan potassium has a short half-life of 2 hr while telmisartan has an extremely long half-life of 24 hr. The antihypertensive effect, however, is consistent across the ARB class and is apparent within two to four weeks after initiation of therapy. In addition, all ARBs are highly protein bound and the mode of elimination for these agents is predominantly by the hepatic route.²⁴

Table 4: PHARMACOKINETIC PROPERTIES OF FDA APPROVED ARBs^{25,26}

Generic Name	Prodrug	Maximal Onset (wk)	Peak (hr)	BA (%)	Food Effect (AUC%)	T _{1/2} (hr)	Protein binding %	P450 Metab	Fecal Elimination %	Urinary Elimination %	Trough: Peak Ratio %	Minimum/Maximum Dosage (mg) Available
Candesartan cilexetil	Yes	2-4	3-4	15	—	9	>99	No	67	33	80	4/32
Eprosartan	No	3	3	13	25	5-9	98	No	90	7	67	400/600
Irbesartan	No	2	1.5-2	60-80	—	12-20	90	Yes	80	20	>60	75/300
Losartan potassium	Yes	2-3	3-4	33	10	2	99	Yes	60	35	58-78	25/100
Telmisartan	No	3	.5-1	42-58	6	24	>99.5	No	98	<1	>97	40/80
Valsartan	No	2	2-4	25	40-50	6	>95	No	83	13	69-76	80/160

BA = bioavailability

Chemistry of Olmesartan Medoxomil

The newest addition to the ARB class is olmesartan medoxomil. Olmesartan medoxomil is a prodrug that is rapidly and completely de-esterified in the intestinal wall into the active metabolite, olmesartan. Olmesartan medoxomil is a non-peptide imidazole derivative.²⁷

Structure-activity studies of imidazole derivatives have reported that a lipophilic biphenyl substituent at the 1-position and a linear alkyl group at the 2-position display strong binding affinities with the hydrophobic pockets of the

angiotensin II receptor. Also, the presence of a tetrazole substituent to the 1-position further enhances antagonist activity.^{20,21}

Olmesartan medoxomil has a tetrazolylbiphenyl group at the 1-position, a propyl group at the 2-position, a hydroxyalkyl substituent at the 4-position, and an ester group at the 5-position.²² (Figure 4) Therefore, based on structure activity studies, the structural characteristics of olmesartan medoxomil may result in enhanced binding to the AT₁ receptor.

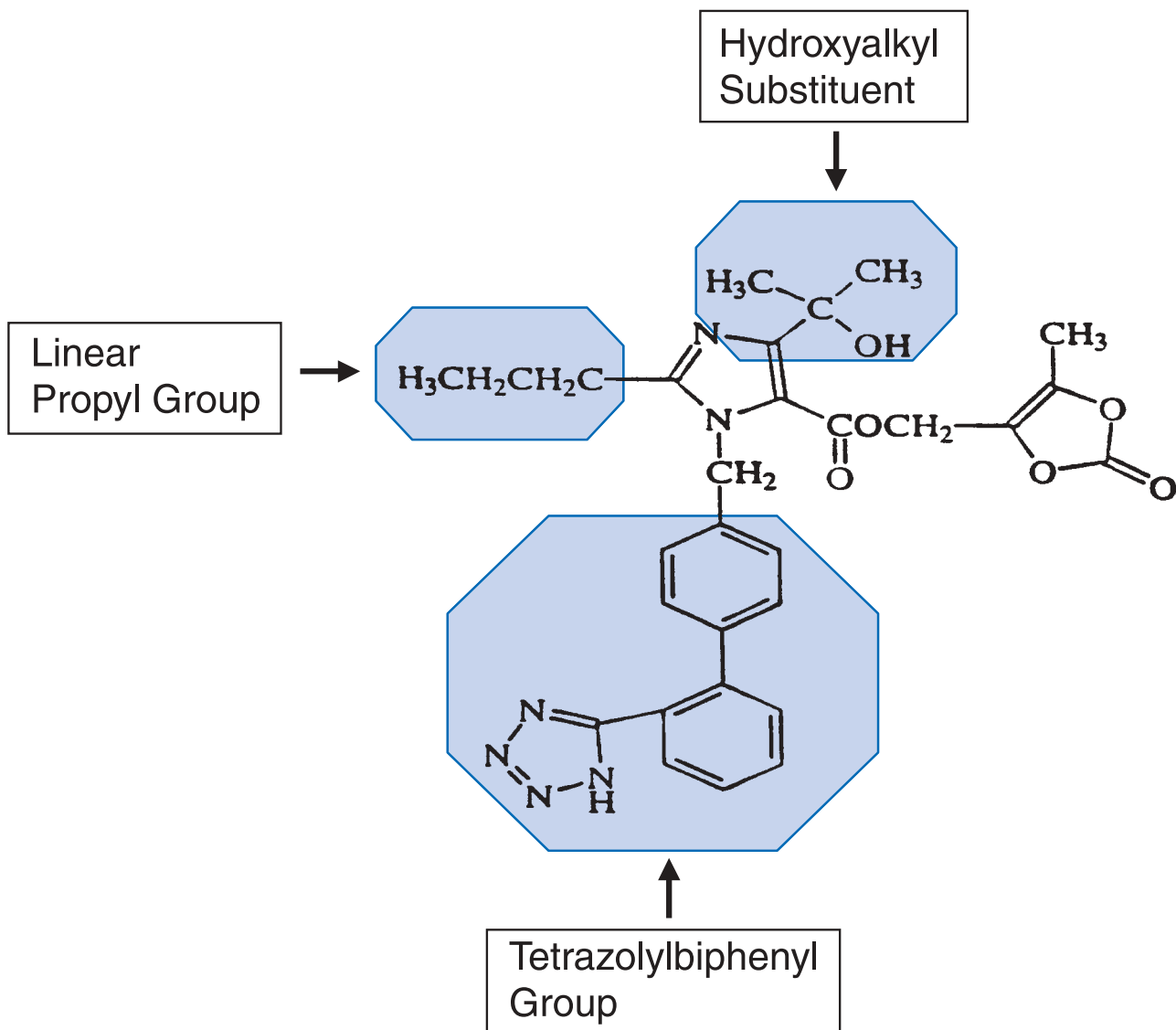


Figure 4: OLMESARTAN MEDOXOMIL STRUCTURAL FORMULA

Clinical Pharmacology of Olmesartan Medoxomil

During presystemic absorption, the prodrug olmesartan medoxomil is de-esterified in the intestinal wall by arylesterase to its active metabolite, olmesartan.²⁹ Olmesartan, the only active metabolite of olmesartan medoxomil, does not undergo any additional metabolism. Olmesartan is a selective, insurmountable AT_1 subtype angiotensin II receptor antagonist.²⁹

Pharmacokinetics of Olmesartan Medoxomil

Olmesartan medoxomil has been shown to exhibit linear pharmacokinetics over dose ranges of 10 to 160 mg. Peak plasma concentrations of olmesartan are rapidly reached in approximately 2 hours after oral dosing with olmesartan medoxomil.¹ The initial antihypertensive response to olmesartan is seen in approximately one week. However, the peak antihypertensive response of olmesartan is generally observed within 2 weeks. The bioavailability of the active metabolite, olmesartan, is 26%.

Olmesartan medoxomil, like other ARBs, is extensively bound to serum albumin (>99%) and α_1 -acid glycoprotein (>96%). Serum albumin binding is inhibited in the presence of warfarin, but not digoxin or diazepam. However, clinical studies have shown that this inhibition had no effect on either the pharmacokinetics or pharmacodynamics of warfarin. The high protein binding of olmesartan accounts for its small volume of distribution of 35 L following oral administration.

Olmesartan medoxomil and the active metabolite, olmesartan, are not metabolized by the cytochrome P450 enzyme system of the liver. Therefore, interactions with concomitantly administered drugs that inhibit, induce, or are metabolized by those enzymes are not expected. No clinically significant, steady-state pharmacokinetic interactions between olmesartan medoxomil were observed with each of the following drugs: digoxin, warfarin, and aluminum magnesium hydroxide.²⁹

Olmesartan has a long terminal elimination half-life of 13 hours, which contributes to the observed 24-hour blood pressure coverage, as well as allowing convenient once-daily administration.

After administration of olmesartan medoxomil, 35% to 50% of the administered dose is eliminated renally, and the remainder is eliminated through the hepatobiliary route. Since olmesartan has a dual mechanism for elimination, dosing modifications are not recommended in patients with mild to moderate renal or hepatic failure.

The pharmacokinetics of olmesartan medoxomil are not altered by food.²⁹

Table 5. OLMESARTAN MEDOXOMIL PHARMACOKINETICS³⁰

Prodrug	Yes
Maximal Onset	2 weeks
Peak Effect	1-2 hours
Duration of Action	24 hours
Bioavailability	26%
Food Effect (AUC%)	————
Volume of Distribution	35 liters
Half-Life	13 hours
Protein Binding	99%
P450 Metabolism	No
Fecal Elimination	50-65%
Urinary Elimination	35-50%
Trough Peak Ratio	51.8-79.1%
Minimum/Maximum Dosage Available	5 mg/40 mg

Safety of Olmesartan Medoxomil

The safety of olmesartan medoxomil has been evaluated in 10 controlled, randomized trials. Seven of the trials were placebo-controlled monotherapy trials that included 2540 patients who were treated with olmesartan medoxomil and 555 patients treated with placebo. The remaining three trials were long-term, placebo-controlled studies that included a total of 1402 olmesartan medoxomil-treated patients and 300 placebo-treated patients. In these studies, olmesartan medoxomil demonstrated an adverse event profile similar to placebo. The most frequently reported adverse events were headache, upper respiratory infections, and influenza-like symptoms, all of which occurred at similar or slightly higher frequencies in placebo-treated patients compared to olmesartan medoxomil-treated patients. The only adverse event reported in the monotherapy placebo-controlled studies with

a higher incidence in patients treated with olmesartan medoxomil versus patients treated with placebo was dizziness (2.8% versus 0.9%, respectively). (Figure 5) The majority of episodes of dizziness were reported to be mild.²⁹

The long-term, placebo-controlled studies evaluating olmesartan medoxomil reported that the occurrence of adverse events was not based on the duration of treatment. In fact, the frequency of adverse events decreased over time, with 50.1% of olmesartan-treated patients experiencing adverse events within the first 12 weeks of treatment, and 26.5% experiencing such events during treatment beyond 39 weeks. (Figure 6) In addition, the overall frequency of adverse events was not found to be dose-related.

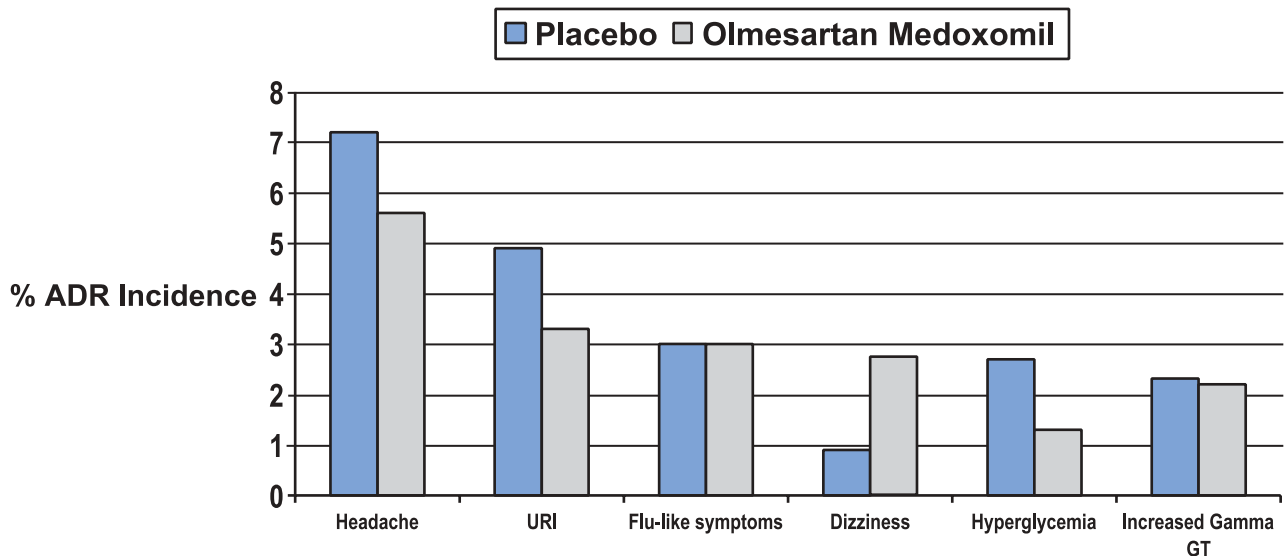


Figure 5: ADVERSE EVENTS REPORTED IN ≥2% OF PATIENTS²⁹

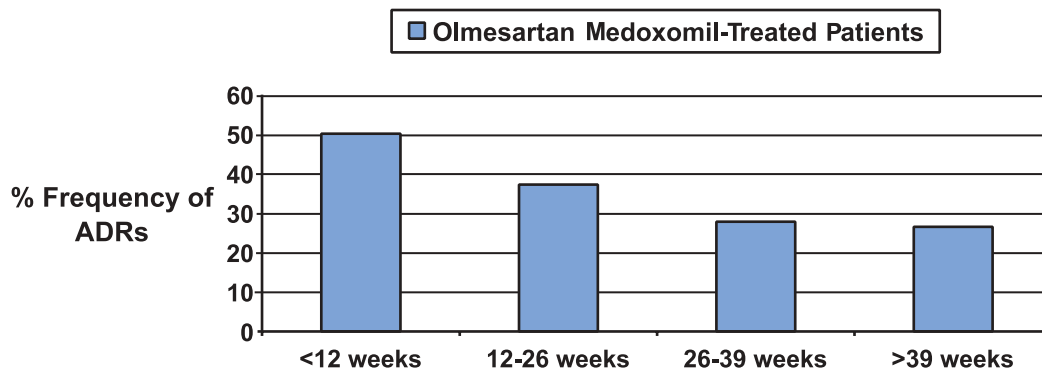


Figure 6: OCCURRENCE OF ADVERSE EVENTS OVER TIME²⁹

Efficacy of Olmesartan Medoxomil

The antihypertensive efficacy of olmesartan medoxomil, at doses ranging from 2.5 to 80 mg, was documented in seven randomized, placebo-controlled, clinical trials studies. An integrated analysis was performed on data from a total of 2693 patients, of which 2145 received olmesartan medoxomil and 548 received placebo. These studies ranged in length from 6 weeks to 12 months.

The primary efficacy variable was defined as the change from baseline in trough sitting diastolic blood pressure (DBP) at the protocol-specific primary study time point (week 6, 8, or 12). Statistical analyses were conducted on an intent-to-treat basis. Olmesartan medoxomil was reported to be significantly more effective than placebo in lowering trough sitting and standing DBP and systolic blood pressure (SBP) at the primary study time point in patients with essential hypertension (defined as a sitting baseline DBP of 100-115 mm Hg.) The reductions in daytime mean SBP and DBP after treatment with 20 mg olmesartan medoxomil were -15 and -12 mm Hg, respectively. (Figure 7)

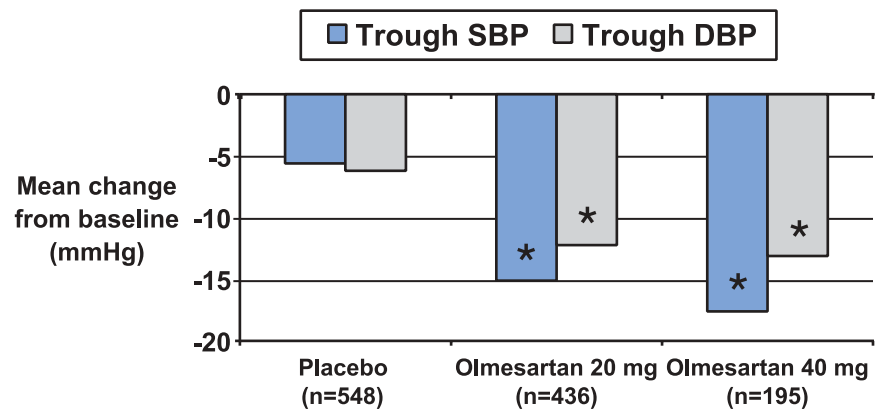


Figure 7: EFFICACY OF OLMESARTAN MEDOXOMIL²⁹

N=1179, treatment period from 6-12 weeks

*P<0.05 versus placebo

A dose-response relationship was observed between olmesartan medoxomil and magnitude of the blood pressure lowering effect over the entire range of doses evaluated (ie, 2.5-80 mg) based on cuff blood pressure. Increasing the dose of olmesartan medoxomil resulted in increased efficacy. Blood pressure lowering effects approached maximum with the 40-mg dose with additional minimal reductions occurring with the 80-mg dose. These dose-response efficacy studies determined that the optimal therapeutic dose range of olmesartan medoxomil was 20-40 mg daily.

Olmesartan medoxomil demonstrated 24-hour blood pressure coverage in an ambulatory blood pressure monitoring (ABPM) study. This was a double-blind, randomized, parallel-group clinical trial. Patients were included in this trial if they had a sitting DBP between 110-115 mm Hg and a mean daytime ABPM diastolic BP \geq 90 mm Hg. The study design consisted of a 4-week run-in period, after which 334 patients were randomized to receive either 5 mg, 20 mg, 80 mg olmesartan medoxomil once daily or 2.5, 10 mg, 40 mg olmesartan medoxomil twice daily, or placebo for 8 weeks. The mean change in ambulatory blood pressure from baseline at last visit demonstrated that olmesartan was efficacious in lowering both SBP and DBP over the entire 24-hour time frame. (Figure 7) In addition, there was no appreciable difference in efficacy observed in this study between once-daily and twice-daily dosing of olmesartan medoxomil. (Figure 8)

Olmesartan medoxomil lowered DBP and SBP values more effectively than placebo regardless of patient age or gender.²

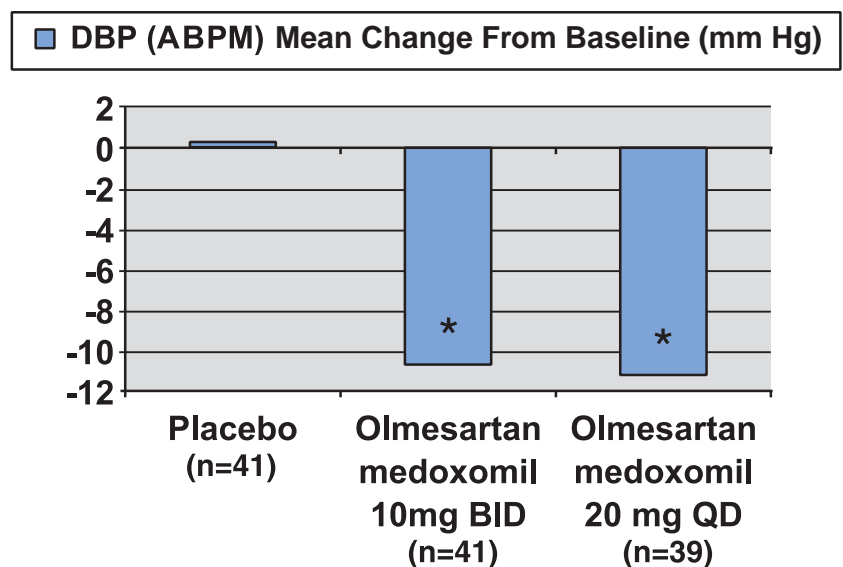


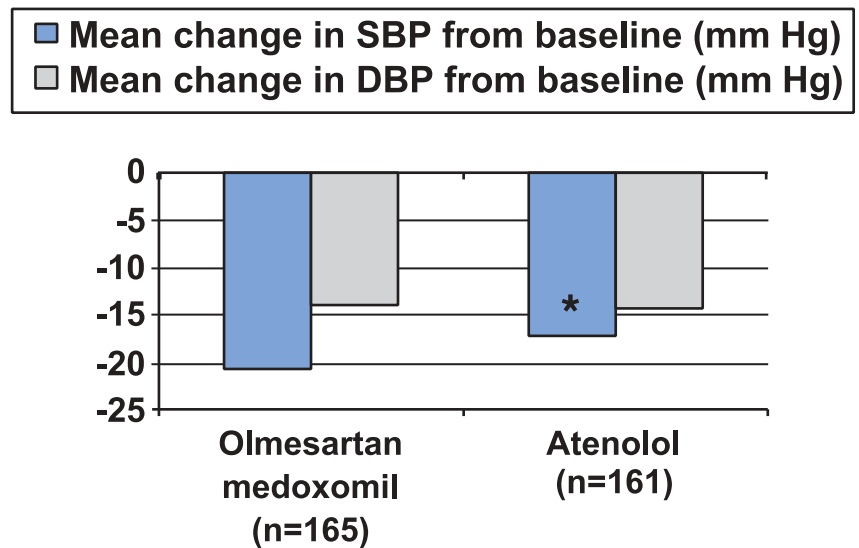
Figure 8: 24-HOUR EFFICACY OF OLMESARTAN MEDOXOMIL²⁹

*P<0.05 versus placebo

Comparison of Other Selected Antihypertensive Agents to Olmesartan Medoxomil

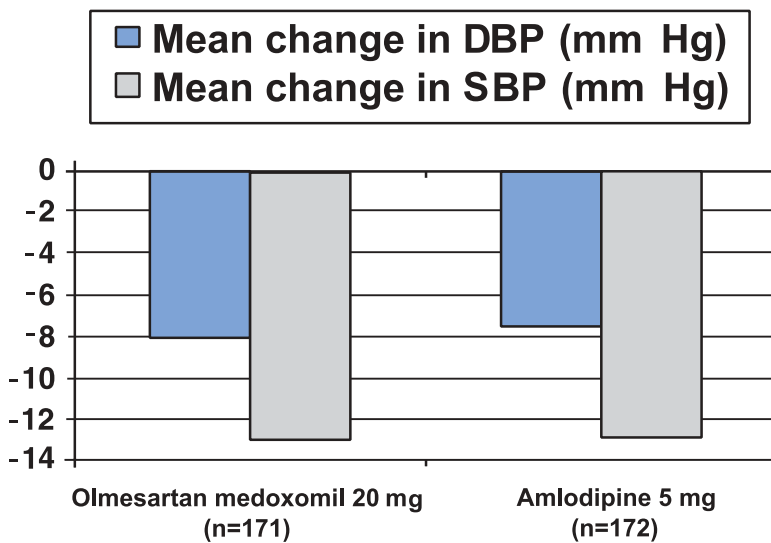
The efficacy of olmesartan medoxomil has been compared to other antihypertensive agents in randomized, double-blind clinical trials. A multi-center (n=326), randomized, double-blind, parallel group, 12-week dose titration trial of olmesartan medoxomil and atenolol was performed in the European Union.²⁹ The primary objective was to assess DBP-lowering effect of up to 20 mg QD of olmesartan medoxomil compared to atenolol dosed up to 100 mg QD. Efficacy for both agents was determined at trough levels (24 ± 2 hours after last dose).

In terms of DBP (primary endpoint), olmesartan medoxomil was shown to produce similar mean reductions to atenolol at 12 weeks (Figure 9). Olmesartan medoxomil had a statistically significantly greater effect in reducing mean SBP than atenolol.



*P<0.05 versus olmesartan medoxomil

Figure 9: Mean reduction in trough SBP and DBP at 12 weeks in patients receiving either olmesartan medoxomil or atenolol²⁹



P=NS olmesartan medoxomil vs amlodipine

Figure 10: Mean change from baseline in SBP and DBP as measured by ambulatory blood pressure monitoring (ABPM) in patients receiving starting doses of olmesartan medoxomil or amlodipine²⁹

The efficacy of the starting dose of olmesartan medoxomil (20 mg QD) was compared to the starting dose of the calcium channel blocker amlodipine (5 mg QD) by ABPM measurements in a placebo-controlled, parallel-group, double-blind study.²⁹ Following a 4-week placebo run-in period, patients (n=431) were randomized to one of three treatment groups and evaluated over the 8-week study period.

As shown in Figure 10, starting doses of olmesartan medoxomil were found to produce mean systolic and diastolic blood pressure reductions similar to the starting dose of amlodipine. While the differences in mean SBP and DBP reductions for olmesartan medoxomil were not statistically significantly different from amlodipine, both active treatment groups were significantly superior to placebo in this study resulting in a statistically significant increase in the number of patients reaching a DBP goal of <85 mm Hg.

Direct Comparison of Selected ARBs

A published, head-to-head clinical study compared the efficacy of starting doses of olmesartan medoxomil, valsartan, losartan, and irbesartan.¹ Patients were included in this study if their cuff DBP was between 100-115 mm Hg and their ABPM daytime DBP was 90 mm Hg or greater. A total of 578 patients met this eligibility criterion. The patients were randomized to the starting dose of one of four treatment arms: olmesartan medoxomil 20 mg, valsartan 80 mg, losartan 50 mg, or irbesartan 150 mg. Patients remained on this monotherapy regimen for eight weeks after which they were evaluated.

The primary endpoint in this study was the change in cuff DBP from baseline to 8 weeks of treatment. In this head-to-head comparative study, olmesartan medoxomil therapy resulted in significantly greater reductions in mean DBP versus valsartan, losartan, or irbesartan. The changes in cuff DBP observed in this trial were: -11.5 mm Hg for olmesartan medoxomil, -9.9 mm Hg for irbesartan, -8.2 mm Hg for losartan, and -7.9 mm Hg for valsartan. (Figure 11)

In addition, significantly more patients responded to, and had their hypertension controlled by, olmesartan medoxomil versus either losartan or valsartan. (Figure 12) The efficacy of olmesartan medoxomil in reducing mean cuff DBP was evident 2 weeks after the initiation of treatment, and was maintained for the duration of the trial.

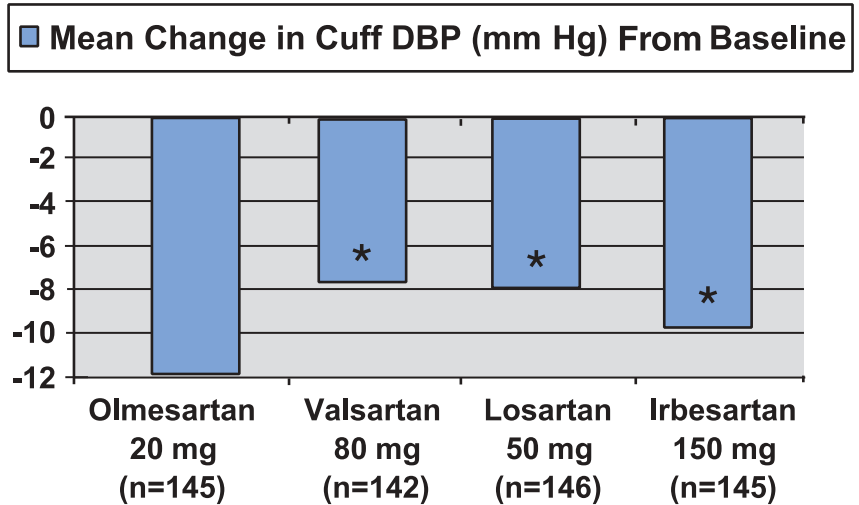


Figure 11: STARTING DOSE ARB COMPARISON STUDY³²

*P<0.05 versus olmesartan medoxomil

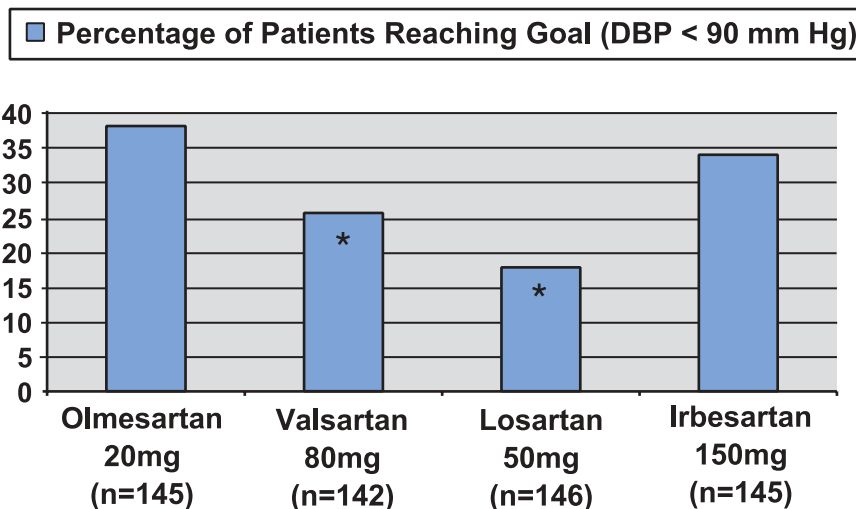


Figure 12: Olmesartan Medoxomil Starting Dose ARB Comparison Study—Percentage of Patients Reaching Goal

*P<0.05 versus olmesartan medoxomil

Conclusion

Despite the numerous antihypertensive agents available, the control of hypertension remains a challenge for health care practitioners. Selective blockers of the angiotensin type I receptor, ARBs, have proven to be important additions to the clinical armamentarium of antihypertensive therapy. ARBs provide effective blood pressure lowering, and an improved tolerability profile when compared to other antihypertensive agents. The improved side-effect profile and convenient once-daily dosing schedule of ARBs contribute to increased patient acceptance of these agents.

Clinical outcome trials have shown ARBs have beneficial effects in special patient populations. For example, RENAAL, IDNT, and IRMA II have all demonstrated that ARBs actually slow progression of renal disease in type II diabetics. The effects of ARBs on cardiovascular morbidity and mortality are currently being evaluated in other clinical outcomes studies. The results from these studies may further define the role of ARBs in the management of hypertension and cardiovascular disease.

Olmesartan medoxomil is a promising new antihypertensive agent in the ARB drug class. Olmesartan medoxomil is not metabolized by the CYP 450 enzyme system, and interactions with concomitantly administered drugs that inhibit, induce, or are metabolized by those enzymes are not expected. Dosing modifications are not necessary in patients with mild to moderate renal or hepatic failure since olmesartan medoxomil has a dual mechanism of elimination. The long terminal elimination half-life and the selective blockade of the AT₁ receptors contribute to the effective 24-hour blood pressure coverage of olmesartan medoxomil after once-daily dosing. In clinical trials, olmesartan medoxomil demonstrated a safety profile similar to placebo. The most frequently reported adverse events in clinical trials were dizziness, headache, upper respiratory infections, and influenza-like symptoms. The antihypertensive efficacy of olmesartan medoxomil was documented in seven randomized, placebo-controlled clinical studies. Olmesartan has shown comparable efficacy to the antihypertensive agents atenolol and amlodipine. Additional studies will further define the role of olmesartan medoxomil in the management of hypertension.

References

- 1 Current Medical Diagnosis and Treatment 2001. 40th edition. SJ McPhee, MA Papadakis, R Gonzales, and LM Tierney Jr, eds. New York: McGraw-Hill; 2001.
- 2 Clinical Hypertension. 6th edition. Kaplan N, Lieberman E, eds. Maryland: Williams and Wilkins; 1994.
- 3 MacMahon SW, Cutler JA, Furberg CD, Payne GH. The effects of drug treatment for hypertension on morbidity and mortality from cardiovascular disease: a review of randomized controlled trials. *Progress in Cardiovascular Diseases*. 1986;XXIX(suppl 1):99-118.
- 4 The sixth report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure. *Archives of Internal Medicine*. 1997;157:2413-2446.
- 5 Givertz, M. Manipulation of the Renin-Angiotensin System. *Circulation*. 2001;31:e14-e18.
- 6 Burnier M, Brunner HR. Angiotensin II receptor blockers. *Circulation*. 2001;103:904-912.
- 7 Willenheimer R, Dahlof B, Rydberg E, Erhardt L. AT1-receptor blockers in hypertension and heart failure: clinical experience and future directions. *European Heart Journal*. 1999;20:997-1008.
- 8 Bloom BS. Continuation of initial antihypertensive medication after 1 year of therapy. *Clinical Therapeutics*. 1998;20:1-11.
- 9 Pitt B, Segal R, Martinez F, et al. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet*. 1997;349:747-752.
- 10 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(9215):1582-1587.
- 11 Cohn JN. Improving outcomes in congestive heart failure: Val-HeFT. Valsartan in Heart Failure Trial. *Cardiology*. 1999;(suppl 1):19-22.
- 12 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. *New England Journal of Medicine*. 2001;345(12):861-869.
- 13 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. *New England Journal of Medicine*. 2001;345(12):851-860.
- 14 Parving HH, Lehnert H, Brochner-Mortensen J, et al. The Effect of Irbesartan on the Development of Diabetic Nephropathy in Patients With Type 2 Diabetes. *New England Journal of Medicine*. 2001;345(12):870-878.
- 15 Dahlöf B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the losartan intervention for endpoint reduction in hypertension study (LIFE): a randomized trial against atenolol. *Lancet*. 2002;359:995-1003.
- 16 Hansson L, Lithell H, Skoog I, et al. Study on Cognition and Prognosis in the Elderly (SCOPE). *Blood Pressure*. 1999;8(3):177-183.
- 17 Mann J, Julius S. The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial of cardiovascular events in hypertension: rationale and design. *Blood Pressure*. 1998;7(3):176-183.
- 18 Pfeffer MA, McMurray J, Leizorovicz A, et al. Valsartan in Acute Myocardial Infarction Trial (VALIANT): rationale and design. *American Heart Journal*. 2000;40:727-734.
- 19 Song J, White CM. Pharmacologic, Pharmacokinetic, and Therapeutic Differences Among Angiotensin II Receptor Antagonists. *Pharmacotherapy*. 2000;20(2):130-139.
- 20 Sica DA. Pharmacology and Clinical Efficacy of Angiotensin Receptor Blockers. *American Journal of Hypertension*. 2001;14:242S-247S.
- 21 Song JC, White CM. Olmesartan Medoxomil (CS-866): an angiotensin II receptor blocker for the treatment of hypertension. *Formulary*. 2001;36:487-499.
- 22 Unger T. Significance of Angiotensin Type I Receptor Blockade: Why Are Angiotensin II Receptor Blockers Different? *American Journal of Cardiology*. 1999; 84:9S-15S.
- 23 Williamson K, Patterson JH, McQueen RH, Adams KF, Pieper JA. Effects of erythromycin or rifampin on losartan pharmacokinetics in healthy volunteers. *Clinical Pharmacology and Therapeutics*. 1998;63(3):316-323.
- 24 Parnell K, Rodgers J, Graff D, Allen T, Hinderliter A, Patterson J, Pieper J. Inhibitory effect of fluconazole and erythromycin plus fluvastatin on losartan. *Clinical Pharmacology and Therapeutics*. 2000;67(2):121.
- 25 Rodgers JE, Patterson JH. Angiotensin II-Receptor Blockers: Clinical Relevance and Therapeutic Role. *American Journal of Health-System Pharmacy*. 2001;58(8):671-683.
- 26 *Drug Facts and Comparisons 2001*. 55th edition. St. Louis, MO: Facts and Comparisons; 2001.
- 27 Grossman E, Messerli FH, Neutel JM. Angiotensin II receptor blockers: Equal or preferred substitutes for ACE inhibitors? *Archives of Internal Medicine*. 2000;160:1905-1911.
- 28 Data on file. Sankyo Pharma. New York, NY.
- 29 Schwocho L, Masonson HN. Pharmacokinetics of CS-866, a New Angiotensin II Receptor Blocker, in Healthy Subjects. *Journal of Clinical Pharmacology*. 2001;41:515-27.
- 30 Von Bergmann K, Laeis P, Puechler K, Sudhop T, Schwocho LR, Gonzalez L. Olmesartan medoxomil: influence of age, renal and hepatic function on the pharmacokinetics of olmesartan medoxomil. *Journal of Hypertension*. 2001;19(suppl 1):S33-S40.
- 31 Oparil S, Williams D, Chrysant SG, Marbury TC, Neutel J. Comparative Efficacy of Olmesartan, Losartan, Valsartan, and Irbesartan in the Control of Essential Hypertension. *The Journal of Clinical Hypertension*. 2001;3:283-291.

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1. According to the Current Medical Diagnosis and Treatment 2001, what percent of patients have their hypertension under control?
 - a. 68%
 - b. 53%
 - c. 27%
 - d. 15%
 - e. 10%
2. According to the JNC-VI guidelines, lifestyle modification should include all of the following except:
 - a. Weight reduction
 - b. Smoking cessation
 - c. Diet modifications
 - d. Sodium restriction
 - e. Folic acid supplementation
3. What was the first drug class used for the treatment of hypertension?
 - a. Calcium channel blockers
 - b. Beta blockers
 - c. ACE inhibitors
 - d. Diuretics
 - e. ARBs
4. JNC-VI recommends which drug class for use in hypertensive patients with concomitant diabetes or heart failure?
 - a. ARBs
 - b. Diuretics
 - c. ACE inhibitors
 - d. Beta blockers
 - e. a and c
5. Which physiologic event can act as a trigger for RAAS?
 - a. A low blood pressure
 - b. A high blood pressure
 - c. An increase in renal blood flow
 - d. A high level of serum Na
 - e. None of the above
6. Which of the following statements about ARBs is false?
 - a. ARBs work by antagonizing the AT₁ receptor
 - b. ARBs prevent the effects of angiotensin II
 - c. ARBs increase bradykinin levels
 - d. All of the above
 - e. None of the above
7. Which clinical trial evaluated the effects of ARBs on the progression of diabetes?
 - a. ELITE I
 - b. Val-HeFT
 - c. IRMA
 - d. SCOPE
 - e. VALUE
8. Which of the following drug classes is contraindicated in pregnancy?
 - a. ARBs
 - b. Beta blockers
 - c. ACE inhibitors
 - d. a and c
 - e. All of the above
9. Which of the following binds the AT₁ receptor surmountably?
 - a. Irbesartan
 - b. Candesartan
 - c. Telmisartan
 - d. Valsartan
 - e. None of the above
10. Which ARB is a prodrug?
 - a. Olmesartan
 - b. Candesartan
 - c. Losartan
 - d. All of the above
 - e. None of the above
11. Which ARB is metabolized by the CYP 450 enzyme system?
 - a. Olmesartan
 - b. Candesartan
 - c. Losartan
 - d. Eprosartan
 - e. None of the above
12. Which ARB substituents would increase the binding affinity to the AT₁ receptor?
 - a. A linear alkyl group at the 2-position
 - b. A hydroxyl group at the 4-position
 - c. A hydrophilic substituent at the 1-position
 - d. None of the above
 - e. All of the above
13. Which adverse event occurred at a higher frequency than placebo in patients treated with olmesartan medoxomil?
 - a. Cough
 - b. Dizziness
 - c. Headache
 - d. Hyperglycemia
 - e. None of the above
14. Olmesartan medoxomil was shown to be as effective as which of the following antihypertensive agents?
 - a. Atenolol
 - b. Amlodipine
 - c. Losartan
 - d. All of the above
 - e. None of the above
15. The head-to-head starting dose clinical trial discussed in this monograph compared olmesartan medoxomil to which of the following ARBs?
 - a. Losartan
 - b. Valsartan
 - c. Irbesartan
 - d. All of the above
 - e. None of the above

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