The Role of Olmesartan Medoxomil-Based Combination Therapy in the Management of Hypertension: A Review for Nurse Practitioners

M Roberts

Citation

M Roberts. *The Role of Olmesartan Medoxomil-Based Combination Therapy in the Management of Hypertension: A Review for Nurse Practitioners*. The Internet Journal of Advanced Nursing Practice. 2012 Volume 11 Number 2.

Abstract

Background: Uncontrolled hypertension increases the likelihood of cardiovascular morbidity and mortality and places a great burden on health care systems. Hypertension (defined as a blood pressure [BP] of greater than (>) 140/90 mm Hg or >130/80 mm Hg in patients with diabetes) is amenable to treatment through lifestyle changes or pharmacological intervention. Although prevalence of hypertension has remained stable through recent years, advances in patient education and the availability of effective antihypertensive agents has allowed patients to better control their BP. Angiotensin II receptor blockers (ARBs) are a widely prescribed class of antihypertensive agents, and the ARB olmesartan medoxomil (OM) has been shown in clinical trials to effectively reduce BP with a placebo-like safety and tolerability profile.Purpose: To review the efficacy of OM-based treatment algorithms in patients with uncontrolled hypertension in specific demographic groups and to discuss the role of the nurse practitioner in the management of hypertension. Conclusions: Nurse practitioners hold a distinctive role at the forefront of primary care, which enables them to identify at-risk patients, ensure accurate diagnosis of hypertension through the proper measurement of BP, provide counseling on lifestyle changes, and prescribe effective pharmacotherapy. Safety and efficacy profiles of OM facilitate its inclusion into combination treatment algorithms when additional antihypertensive agents are needed to achieve desirable BP control. Clinical Implications: Clinical practice guidelines have established the paradigm that treating patients to defined BP goals may enable better patient outcomes. However, not all patients are managed to established goals. Issues of adherence, regimen complexity, and recognition of the need to escalate from monotherapy to combination therapy are common barriers to effective patient management.

INTRODUCTION

According to data from the 1999–2008 National Health and Nutrition Examination Survey (NHANES), an estimated 29% of Americans aged ≥18 years are presently living with hypertension,[1] with another 28% of American adults classified as being at risk of developing the disease.[2] Stage 1 hypertension, defined as a systolic blood pressure (SBP) of 140–159 mm Hg or a diastolic blood pressure (DBP) of 90–99 mm Hg, affects an estimated 25 million adults in the United States.[3] Stage 2 hypertension (SBP ≥160 mm Hg or DBP ≥100 mm Hg) is more common in the elderly and in Blacks. Poorly controlled hypertension is associated with many adverse cardiovascular and cerebrovascular outcomes and contributes a substantial financial burden to the healthcare system.[4] Nurse practitioners have a unique opportunity to positively impact the national standard of care for patients with hypertension. These opportunities arise from their ability to effectively communicate complex medical information to patients, especially the risks associated with medical non-compliance.

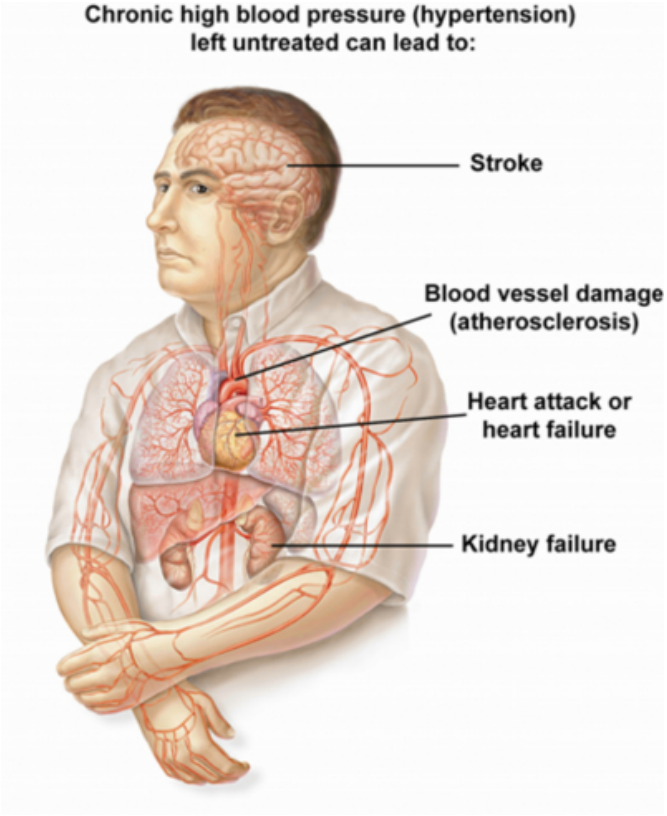
CLINICAL CONSEQUENCES OF UNCONTROLLED HYPERTENSION

The major long-term concern of uncontrolled hypertension is damage to organs such as the heart, brain, and kidneys, which may increase patient morbidity and mortality (see Figure 1). The risk of death due to stroke or ischemic heart disease (angina, myocardial infarction [MI], and heart failure) is estimated to double with every 20-mm Hg increase in SBP >115 mm Hg and with every 10-mm Hg increase in DBP >75 mm Hg.[5] Hypertension causes higher after-load pressures in the arterial vasculature that blood must be pumped against. Myocardial hypertrophy may lead to heart failure resulting in reduced ejection fraction and decreased end-organ perfusion. Manifestations of left-sided

heart failure include pulmonary congestion, orthopnea, exercise intolerance, and dyspnea at rest. Angina is also likely, with myocardial thickening due to an imbalance between myocardial oxygen demand and blood supply.

Figure 1

Figure 1. Sites of hypertension-associated morbidity



Uncontrolled hypertension greatly increases the risk of embolic and hemorrhagic stroke. In an Australian study evaluating major risk factors of intracerebral hemorrhage, patients with hypertension were 2.5 times more likely to experience stroke than patients who were not hypertensive.[6] Sustained elevated blood pressures (BPs) are also associated with renal complications and elevated serum creatinine levels.[7,8] Sustained elevated BP is of particular concern to patients who have diabetes mellitus, where the risk of end-stage renal disease is estimated to be five to six times higher than patients who have diabetes without hypertension.[9]

THE NURSE PRACTITIONER'S ROLE IN PATIENT MANAGEMENT

Nurse practitioners and other clinicians in a variety of practice settings have the opportunity to identify patients who are at risk of developing hypertension and to ensure that patients with hypertension are not left untreated or undertreated.[10] A common barrier to effective hypertension management is the lack of patient adherence to treatment regimens. As many as 40%–50% of patients with cardiovascular disease (CVD) and hypertension do not follow their prescribed regimens.[11,12] Furthermore, an increased duration of therapy for chronic conditions has been correlated with decreased adherence.[13,14] Simplifying hypertension treatment through the use of fixed-dose combination therapy has helped to increase BP control in patients.[15] Nurse practitioners who counsel patients on lifestyle modifications and good health practices, as well as prescribe medication regimens that take into account issues of adherence, can bring the best of evidence-based medical care of hypertension to their patients.

MANAGEMENT OF HYPERTENSION

LIFESTYLE MODIFICATIONS

The management of hypertension usually begins with lifestyle modifications.[4] A 10-pound reduction of body weight may reduce BP or prevent hypertension altogether.[4] In a randomized controlled trial (RCT) of 181 patients, the mean SBP reduction associated with weight loss over an 18-month period was 6.9–13.3 mm Hg.[16] Patients can be counseled that proper weight reduction is achieved by eating a healthy diet and by increasing daily physical activity. The Dietary Approaches to Stop Hypertension (DASH) eating plan is recognized by the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) guidelines as a diet that can help lower BP. DASH consists of a diet high in fruits, vegetables, and low-fat dairy products, while avoiding or minimizing foods that are high in saturated fat or cholesterol (red meat, fried foods, etc.). Dietary sodium reduction complements the DASH diet. A sodium intake of less than (<) 2.4 grams/day in combination with the DASH diet has been shown to reduce SBP by 11 mm Hg in one clinical trial.[17] Alcohol reduction is also advised to improve hypertension. In a meta-analysis of 15 RCTs, moderation of alcohol intake resulted in a 2–4-mm Hg SBP reduction.[18]

Regular exercise and smoking cessation are also recommended lifestyle modifications for hypertensive patients. Patients, who are physically capable, should exercise for 30 minutes per day most days of the week.[4] In two separate meta-analyses of RCTs, patients who engaged in either aerobic exercise or resistance training programs were found to have BP reductions ranging from 4–9 mm Hg.[4,19] Finally, smoking cessation should be encouraged to

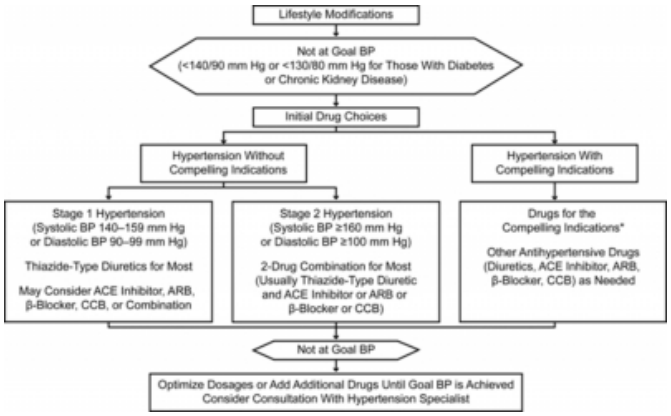
patients as smoking is a known cardiovascular risk factor.[4]

PHARMACOTHERAPY OF STAGE 1 AND 2 HYPERTENSION

The pharmacologic management of hypertension is based on severity and the presence of compelling indications (diabetes, chronic kidney disease, heart failure, post-MI, high coronary disease risk, and recurrent stroke prevention).[4] For most patients, a target BP goal is ≤140/90 mm Hg. For patients who have diabetes or chronic kidney disease, the BP goal is ≤130/80 mm Hg. Monotherapy is recommended initially for patients with stage 1 hypertension.

Figure 2

Figure 2. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) treatment algorithm.



*Heart failure = diuretic, β-blocker, ACE inhibitor, ARB, aldosterone antagonist; post-myocardial infarction = β-blocker, ACE inhibitor, and aldosterone antagonist; high coronary disease risk = diuretic, β-blocker, ACE inhibitor, CCB; diabetes = diuretic, β-blocker, ACE inhibitor, ARB, CCB; chronic kidney disease = ACE inhibitor, ARB; recurrent stroke prevention = diuretic, ACE inhibitor.

Available at http://www.nhlbi.nih.gov/guidelines/hypertension/jnc7full.pdf.

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BP, blood pressure; CCB, calcium channel blocker.

In the JNC 7 treatment algorithm for patients without compelling indications, the treatment of choice is a thiazide-type diuretic (hydrochlorothiazide [HCTZ] or chlorthalidone)[4] (see Figure 2). If BP goals are not reached with thiazide-type diuretics alone, then thiazides may be given in combination with other antihypertensive medications including angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), calcium channel blockers (CCBs), beta (β)-blockers, and aldosterone antagonists. Other classes of medications apart from thiazide diuretics are not recommended by JNC 7 as initial monotherapy in patients without compelling indications, although studies have shown that ACE inhibitors, ARBs, CCBs,

β-blockers,[20] and aldosterone antagonists[21] are also effective choices as initial monotherapy. The data supporting the use of other classes of medications as initial monotherapy are also confirmed by the 2009 reappraisal of the European Society of Hypertension/European Society of Cardiology (ESH/ESC) 2007 guidelines, which recommend the use of thiazide diuretics, ACE inhibitors, ARBs, CCBs, and β-blockers as first-line therapy.[22] Updated guidelines from the American Diabetes Association (ADA) recommend ARBs or ACE inhibitors as monotherapy for initial antihypertensive therapy in patients with diabetes.[23] For patients with stage 2 hypertension or those who are high risk and require more rapid BP lowering, initiating treatment with a thiazide-type diuretic plus a second agent is recommended.[4] Drugs should be initiated at lower doses and titrated carefully to avoid hypotension and other adverse effects. More recently, fixed-dose combinations of ARBs and CCBs have been approved as first-line antihypertensive medications in patients who are unlikely to achieve their BP goals with monotherapy.

BLOOD PRESSURE MEASUREMENT

Traditionally, BP is assessed with seated cuff measurements. Ideally, a seated cuff BP (SeBP) measurement is performed after the patient has been at rest for 3–5 minutes.[24] Appropriately sized BP cuffs should be used for both obese and pediatric patients, and care must be taken to assure that the patient's rolled-up sleeve is not acting as a tourniquet. Two BP measurements taken 1 minute apart, with the average of the two values recorded as the patient's final BP, is recommended. If a difference of >5 mm Hg exists between both measurements, then an additional one or two measurements should be taken with the average of all measurements used as the final result.[24]

Ambulatory BP monitoring (ABPM) has several advantages over SeBP monitoring. BP values fluctuate naturally according to a circadian profile,[25] and ABPM allows the

clinician to obtain the average of multiple BP measurements rather than the average of 2–3 readings obtained in one clinical appointment. Secondly, ABPM measurements have been shown to have a closer association with target organ damage than SeBP measurements.[26] Patients who do not have a decrease in BP during the sleeping hours are more likely to experience cardiovascular events. Similarly, most patients are at a higher risk during the morning hours when BP surges are common. ABPM can help to identify the magnitude of these nighttime and morning BP fluctuations. At present, the JNC 7 guidelines recommend that ABPM be used for suspected white-coat hypertension, apparent drug resistance, hypotensive symptoms while on medication, and for episodic hypertension and autonomic dysfunction.[4]

The use of ABPM and home BP monitoring (HBPM) has been elevated more recently into the role of helping to confirm a diagnosis of hypertension. The National Institute for Health and Clinical Excellence (NICE) released new hypertension guidelines for 2011 that state that ABPM and HBPM average daily values of ≥135/85 mm Hg are confirmatory of a clinical diagnosis of hypertension.[27] The American Heart Association (AHA), American Society of Hypertension, and Preventive Cardiovascular Nurses Association, in a joint statement, recommended that HBPM become part of the routine BP measurement regimen in patients with known or suspected hypertension.[28] HBPM can help solidify a diagnosis, monitor response to treatment, and may help improve adherence to therapy.

DISEASE MANAGEMENT IN POPULATIONS WITH DIFFICULT-TO-TREAT HYPERTENSION

Common subgroups of patients with difficult-to-treat hypertension include the elderly, obese, diabetics, Blacks, and patients with metabolic syndrome. Patients from these subgroups and those with multiple comorbidities are often difficult to treat.[4,29-31]

THE ELDERLY

The incidence of hypertension has been shown to increase in both males and females as patients age.[32] Effective and focused treatment of hypertension in the elderly is associated with reduced primary outcomes such as stroke, MI, or non-MI cardiac death.[33,34] One challenge in treating the elderly is BP variability. During morning hours, the elderly are likely to have BP surges that place them at increased risk for cardiovascular and cerebrovascular events.[25,35] Adequate BP control regimens must take BP variability and the morning BP surge into account. Elderly patients are also prone to sudden drops in BP with changes in position. Medications whose effects are sustained throughout the day can help to minimize this orthostasis. Finally, the elderly are very likely to require multiple agents to reach BP goals, which add to increased pill burden for other conditions treated concomitantly. Fixed-dose combination products can be very helpful in minimizing pill burden in the elderly, provided that patients can tolerate multiple antihypertensives. The 2011 Expert Consensus Document on Hypertension in the Elderly encourages that medication therapy be initiated at the lowest possible dose and then gradually titrated upwards.[36] A BP target of <140/90 mm Hg is recommended, provided that the doses and medications required to reach this BP target are tolerated by the patients. In patients who are aged ≥80 years, an SBP of 140–145 mm Hg should be regarded as acceptable. However, a BP of <130/65 mm Hg should generally be avoided in patients ≥80 years of age due to concerns about inadequate organ perfusion.[36]

PATIENTS WITH DIABETES

Hypertension occurs in patients with type 2 diabetes at an estimated rate of 77%.[37] Patients with diabetes are at risk for both microvascular and macrovascular complications, outcomes that are highly dependent on adequate BP control. In at least one study evaluating data from NHANES, only 35.3% of patients with diabetes who were treated for hypertension were found to be at BP goal.[37] The ADA and JNC 7 guidelines point out that achieving BP goals may be difficult in this population and that patients may require two to three antihypertensive agents.[4,23] Both sets of guidelines recommend the use of an ACE inhibitor or ARB in a combination treatment regimen due to their demonstrated ability to reduce the incidence of albuminuria and the progression of nephropathy.[38] Along with the elderly, pill burden and poor adherence to medical therapy are barriers to treatment for this subgroup, as patients with diabetes may also be treated concomitantly for dyslipidemia, poor glucose control, and many other conditions.

More recently, some debate has occurred about the appropriateness of the JNC 7-recommended BP goal of <130/80 mm Hg in patients with type 2 diabetes. The 2009 reappraisal of the 2007 ESH/ESC guidelines examined clinical trials that showed a positive benefit on primary endpoints with BP lowering.[22] In patients with type 2 diabetes, the mean SBP achieved in trials with positive primary outcomes ranged from 134–153 mm Hg, above the

JNC 7-recommended SBP target of <130 mm Hg. The ACCORD (Action to Control Cardiovascular Risk in Diabetes) BP study and a post-hoc analysis of INVEST (International Verapamil SR-Trandolapril Study) both demonstrated that targeting an SBP <130 mm Hg was not associated with statistically significant reductions in primary outcomes, but was associated with increased mortality, although not statistically significant.[39,40] Finally, a recent meta-analysis by Bangalore et al. concluded that aggressive SBP goals of <130 mm Hg lowered the risk of stroke but offered no benefit in reducing the risk of cardiac, renal, or retinal endpoints.[41] The upcoming release of JNC 8 guidelines may provide additional guidance in this area.

BLACKS

Blacks have been shown to have higher rates of hypertension including hypertension that is considered severe (≥180/110 mm Hg).[42] In addition, Blacks have been shown to have less nighttime decreases in BP compared with Caucasians.[4] Normally, nighttime BPs drop by 10%–20% from 12 p.m.–6 a.m. ABPM measurements have shown that Blacks often experience nighttime BP reductions of <10%.[42] In Blacks, it is common to see stage 2 hypertension, increasing the risk for target organ damage occurring earlier in life. Data from the National Center for Health Statistics have shown higher incidences of CVD, renal disease, and all-cause mortality in Blacks relative to Caucasians.[43] A 2010 update of the International Society on Hypertension in Blacks (ISHIB) Consensus Statement affirms the need to reverse the accelerating prevalence of hypertension in this population.[42]

ISHIB classifies patients with hypertension by two risk categories: primary prevention and secondary prevention.[42] Primary prevention groups are patients with high BP with no evidence of end-organ damage, preclinical or current CVD, and who have a goal BP of <135/85 mm Hg. Secondary prevention groups are patients who have high BP with target organ damage, preclinical CVD, or a history of CVD. The same six compelling indications in JNC 7 guidelines define secondary prevention groups in the ISHIB 2010 guidelines with the exception of the addition of coronary heart disease or angina as a seventh compelling indication. Patients in the secondary prevention risk category have a goal BP of <130/80 mm Hg.

In the primary prevention group, treatment with a diuretic or CCB is recommended as initial therapy when lifestyle modifications do not achieve desired goals.[42] In primary prevention patients whose SBP is >15 mm Hg and/or DBP >10 mm Hg above goal, two-drug therapy with a CCB plus a renin–angiotensin system (RAS) blocker or a thiazide and RAS blocker combination should be considered. In the secondary prevention group, initial monotherapy in patients who are <15/10 mm Hg above the goal BP of <130/80 mm Hg should include an agent that is appropriate to treat the compelling indication. In secondary prevention patients whose BP is >15/10 mm Hg over the goal BP of <130/80 mm Hg, combination therapy including an agent appropriate for the compelling indication is preferred.

PATIENTS WITH METABOLIC SYNDROME

The most recent AHA/National Heart, Lung, and Blood Institute guidelines describe metabolic syndrome as a combination of metabolic risk factors that predispose a patient to atherosclerotic CVD.[44] Metabolic risk factors include hypertension, dyslipidemia, and elevated blood sugar. Underlying risk factors further contributing to metabolic syndrome include aging, abdominal obesity, physical inactivity, and hormonal imbalance. Patients with elevated BP and metabolic syndrome are recommended to initiate lifestyle modifications once BP is ≥120/80 mm Hg.[44] Healthy lifestyle modifications are similar to recommendations in the JNC 7 treatment guidelines—DASH diet, sodium restriction, moderation of alcohol consumption, weight control, and increased exercise.[4] Pharmacological treatment is initiated once BP is ≥130/80 mm Hg in patients with chronic kidney disease or diabetes, and once BP is ≥140/90 mm Hg for all others. Treatments using ACE inhibitors or ARBs are appropriate choices in patients with metabolic syndrome due to their renoprotective and cardioprotective effects.[45] A meta-analysis of 12 RCTs showed that ACE inhibitors and ARBs reduced the progression of study subjects to type 2 diabetes by 25% (95% confidence interval, 0.69–0.82).[46] Patients included in this analysis had hypertension, metabolic syndrome, or at least one cardiovascular risk factor at baseline.

THE NEED FOR COMBINATION THERAPY

Most clinical trials investigating the efficacy of antihypertensive therapy on endpoints such as stroke or cardiovascular events have generally allowed for a combination of agents to be used in order to bring study subjects to BP goals. BP control rates in study populations are as low as 27%–37% at baseline on monotherapy and as high as 53%–75% at study conclusion when multiple agents

are used and/or optimized.[47-49] In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), patients were randomized to monotherapy utilizing chlorthalidone, amlodipine (AML), or lisinopril. At study close, 67% of patients achieved an SBP of <140 mm Hg, and 63% of those study subjects required two or more medications to reach their goal.[47] Nurse practitioners must be cognizant that, for most patients, monotherapy will be a stepping stone to combination therapy in order to achieve BP goals.

FIXED-DOSE COMBINATION THERAPY

Fixed-dose combination therapy can be regarded as taking combination therapy to a new level. Advantages of improved efficacy over monotherapy are offered while providing the added benefit of simplification of the BP control regimen using a single pill. Many fixed-dose combinations build upon a single agent by adding on one or two additional classes of antihypertensives. As fixed-dose combinations are available that contain different doses of the individual component agents, different dose combinations can be selected while retaining the convenience of a single pill. Fixed-dose combination treatment has been shown to increase persistence and adherence.[22] In addition, fixed-dose combination therapy demonstrates similar or even improved tolerance, as one component may sometimes offset the deleterious effects of another.[22] Nurse practitioners may consider fixed-dose combination therapy as the first option for patients to improve adherence with medical therapy.

OLMESARTAN MEDOXOMIL

Olmesartan medoxomil (OM) is an ARB approved by the US Food and Drug Administration (FDA) in April 2002 for the management of hypertension in adults when used as monotherapy or in combination with other antihypertensive agents.[50] Olmesartan, the active metabolite, has a half-life of approximately 13 hours[50] compared with the shorter half-lives of other commonly prescribed ARBs such as valsartan (6 hours)[51] and losartan (2 hours) [active metabolite EXP-3174 6–9 hours].[52] In February 2010, the FDA revised labeling to include the indication of the management of hypertension in pediatric patients aged 6–16 years. Olmesartan is available as monotherapy (Benicar®), in dual fixed-dose combinations with HCTZ (Benicar HCT®) or AML (Azor®), and as a triple single-pill combination with all three agents (Tribenzor™). The dosing of OM-based combination therapy and other ARB-based fixed-dose combination therapies are presented below.

Figure 3

Table 1. Dosing information of ARB-based fixed-dose combinations

Generic Name(s)	Trade Name	Dosage Form Availability (mg)	Starting Daily Dose (mg)
Azilsartan			
Azilsartan/chlorthalidone[53]	Edarbyclor®	40/12.5 and 40/25	40/12.5
Candesartan			
Candesartan/HCTZ[54]	Atacand HCT®	16/12.5, 32/12.5, and 32/25	Based on monotherapy[a]
Eprosartan			
Eprosartan/HCTZ[55]	Teveten HCT®	600/12.5 and 600/25	600/12.5
Irbesartan			
Irbesartan/HCTZ[56]	Avalide®	150/12.5 and 300/12.5	150/12.5
Losartan			
Losartan/HCTZ[57]	Hyzaar®	50/12.5, 100/12.5, and 100/25	50/12.5
Olmesartan			
OM/HCTZ[58]	Benicar HCT®	20/12.5, 40/12.5, and 40/25	Based on monotherapy[a]
AML/OM[59]	Azor®	5/20, 5/40, 10/20, and 10/40	5/20
AML/OM/HCTZ[60]	Tribenzor®	20/5/12.5, 40/5/12.5, 40/5/25, 40/10/12.5, and 40/10/25	Based on combination therapy[a]
Telmisartan			
Telmisartan/HCTZ[61]	Micardis HCT®	40/12.5, 80/12.5, and 80/25	Based on monotherapy[a]
Telmisartan/AML[62]	Twynsta®	40/5, 40/10, 80/5, and 80/10	40/5
Valsartan			
Valsartan/HCTZ[63]	Diovan HCT®	80/12.5, 160/12.5, 160/25, 320/12.5, and 320/25	160/12.5
AML/valsartan[64]	Exforge®	5/160, 10/160, 5/320, and 10/320	5/160
AML/valsartan/HCTZ[65]	Exforge HCT®	5/160/12.5, 10/160/12.5, 5/160/25, 10/160/25, and 10/320/25	5/160/12.5
Aliskiren/valsartan[66]	Valturna®	150/160 and 300/320	150/160

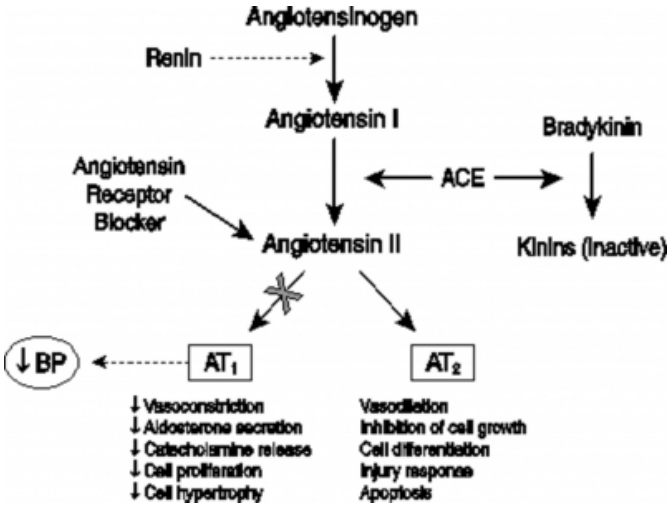
[a]Drug label recommends starting with the lowest dose of the component that the patient is not currently taking

OLMESARTAN MECHANISM OF ACTION

BP control in the body is regulated by the renin–angiotensin–aldosterone system (RAAS). Renin is released by the kidneys due to BP decreases, decreased sodium chloride levels in the renal filtrate, and from increased sympathetic nervous system activity.[67] Renin converts angiotensinogen, which is produced in the liver, to its active form angiotensin I (see Figure 3). Angiotensin I is then converted to angiotensin II by ACE in the lungs. Angiotensin II is a potent vasoconstrictor, which upon binding to the angiotensin I (AT_1) receptor, causes arterial constriction and an increase in BP. Effects of the receptor binding are not limited directly to the blood vessel. Angiotensin II also causes an increase in the synthesis and release of aldosterone from the kidneys, which increases sodium and water retention in the blood. BP rises due to the increased blood volume.

Figure 4

Figure 3. The antihypertensive effects of angiotensin receptor blockers.



Reprinted with permission from Mire DE, et al. J Cardiovasc Pharmacol. 2005;46(5):585-593. ACE, angiotensin-converting enzyme; BP, blood pressure.[67]

ARBs such as OM are classified alongside ACE inhibitors as RAS inhibitors; however, both classes of medications act by differing mechanisms. ACE inhibitors block the conversion of angiotensin I to angiotensin II, while ARBs block the binding of angiotensin II at its AT_1 receptor site. Other differences in the mechanisms of action include interaction with the bradykinin and substance P degradation pathways. ACE inhibitors are believed to impede the degradation of bradykinins and substance P in the lungs, while the receptor-blocking mechanism of ARBs does not interfere with the degradation of these substances. Because of these differences, an estimated 5%–35% of patients are unable to tolerate ACE inhibitors due to a chronic, nagging dry cough.[68] Common adverse events shared by both ACE inhibitors and ARBs include hypotension, dizziness, headache, and fatigue.[50,69] Mild and transient hyperkalemia is possible, though often resolves with continued therapy, and can be minimized by avoidance of concomitant use of potassium-sparing diuretics or potassium supplements.[50,69] Rare and potentially life-threatening adverse events associated with ACE inhibitors and ARBs include angioedema and acute renal failure in patients with renal insufficiency.[50,69]

EFFICACY AND SAFETY OF OLMESARTAN MEDOXOMIL/HCTZ

Thiazide diuretics add additional BP-lowering effects to OM by reducing blood volume through the excretion of sodium and chloride ions into the renal filtrate.[58] The combination of OM and HCTZ has been evaluated in a variety of clinical trials, and key trial data are summarized in Table 2.

Figure 5

Table 2. Key findings of clinical trials with olmesartan-based combination therapy

Study	N	Cohort	End-of-Study (Max Dose) SeBP Reduction (mm Hg)	End-of-Study SeBP Goal Achievement (%)
Chrysant et al. 2004	502	HTN	26.8/21.9 (OM/HCTZ 40/25 mg)	87.2 (SBP <140 mm Hg) 79.5 (DBP <90 mm Hg)
BENISILVER Kereiakes et al. 2009	178	Elderly with HTN	25.8/11.0 (OM/HCTZ 40/25 mg)	67.0 (BP <140/90 mm Hg) 42.6 (BP < 130/80 mm Hg)
BENIFORCE Oparil et al. 2008	276	Stage 1 & 2 HTN	23.2/12.3 (OM/HCTZ 40/25 mg)	74.1 (BP <140/90 mm Hg)
COACH Chrysant et al. 2008	1940	HTN	28.5/19.4 (AML/OM 10/40 mg)	53.2 (BP <140/90 or <130/80 mm Hg for T2DM)
COACH Extension Chrysant et al. 2009	1684	HTN	36.1/19.8 (AML/OM 10/40 mg + HCTZ 25 mg)	66.7 (BP <140/90 or <130/80 mm Hg for T2DM)
TRINITY Oparil et al. 2010	2492	HTN	37.1/21.8 (AML/OM 10/40 mg + HCTZ 25 mg)	69.9 (BP <140/90 mm Hg)
BP-CRUSH Weir et al. 2011	999	Prior failed monotherapy	25.1/13.7 (AML/OM 10/40 mg + HCTZ 25 mg)	77.1 (BP <140/90 mm Hg)

AML, amlodipine; BP, blood pressure; HCTZ, hydrochlorothiazide; HTN, hypertension; OM, olmesartan medoxomil; SeBP, seated cuff BP; T2DM, type 2 diabetes mellitus.

The pivotal US study for approval of OM/HCTZ combination therapy was a randomized, double-blind factorial study in 502 patients.[70] Following a 4-week placebo run-in period, patients were randomized to one of 12 possible treatment groups for a period of 8 weeks. Treatment groups consisted of OM monotherapy (10, 20, or 40 mg/day), HCTZ monotherapy (12.5 or 25 mg/day), any combination of the OM and HCTZ monotherapy doses, or placebo. Mean trough SeBP was reduced by –3.3/–2.8 mm Hg, –20.1/–16.4 mm Hg, and –26.8/–21.9 mm Hg for placebo, OM/HCTZ 20/12.5 mg, and OM/HCTZ 40/25 mg, respectively. Combination therapy provided greater BP reductions compared with OM and HCTZ given as monotherapy. In addition, OM/HCTZ was found to be well tolerated with an overall discontinuation rate due to adverse effects of 2%. The efficacy of OM/HCTZ in subpopulations of interest is discussed below.

The BeniSILVER (Benicar Efficacy: New Investigation

Shows Olmesartan Medoxomil Treatment Increasingly Leads Various Elderly Populations to Safe BP Reductions) study demonstrated efficacy of OM/HCTZ treatment in a difficult-to-treat population.[71] Following a placebo run-in period, 178 elderly patients were treated with OM monotherapy before being up-titrated every 3 weeks to a maximum dose of OM/HCTZ 40/25 mg if SeBP was ≥120/70 mm Hg. In total, 159 patients required titration to combination therapy, and the mean ambulatory BP decreased from 148.8/80.9 mm Hg to 123.1/68.6 mm Hg by study end. Reductions from baseline were found to be statistically significant throughout the 24-hour dosing interval ($P < 0.0001$).[71]

The BENIFICIARY (Benicar Safety and Efficacy Evaluation: an Open-label Single-arm, Titration Study in Patients with Hypertension and Type 2 Diabetes) study investigated the efficacy and safety of OM/HCTZ in patients with diabetes and hypertension with a real-world dose-titration, open-label study design.[72] By study end, 24-hour ambulatory SBP decreased from 146.4 mm Hg to 126.0 mm Hg, a statistically significant decrease of –20.4 mm Hg from baseline ($P < 0.0001$).[72] Overall, 61.6% of patients achieved a 24-hour ambulatory SBP target of <130 mm Hg. Ambulatory monitoring of SBP in this trial demonstrated that BP remained below 130/80 mm Hg for 70.9% of patients during the last 6 hours of the dosing interval when BP normally rises (see Figure 4). Patients with diabetes are at an increased risk of cardiovascular events that have been shown to be more frequent in the morning, before the next dose.[35] Drug-related treatment-emergent adverse events (TEAEs) occurred at a rate of 7.6% at the OM/HCTZ dose of 40/25 mg. The most frequent drug-related TEAEs reported included fatigue (1.4%) and vertigo, chest discomfort, and edema (all 0.7%).

Figure 4. Hourly mean systolic BP (SBP) and diastolic BP (DBP) at baseline and following 12 weeks of treatment with olmesartan medoxomil ± hydrochlorothiazide in patients with diabetes and hypertension in the BENIFICIARY study. Blood pressure (BP) changes during the 24-hour dosing interval and treatment reduced BP throughout the dosing interval including the morning BP surge. End-of-study mean 24-hour ambulatory BP was 126.0/72.2 mm Hg compared with 146.4/83.3 mm Hg at baseline.[72]

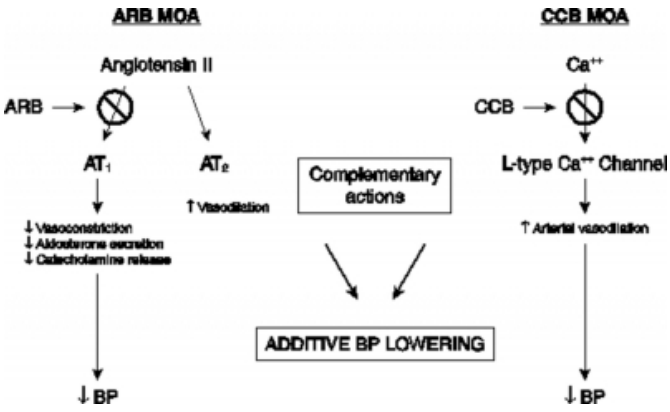
The BENIFORCE (Benicar Efficacy: New Investigative Findings Show Olmesartan Medoxomil Safely and Effectively Reduces Blood Pressure Compared With Placebo in a Clinical Evaluation of Patients With Stage 1 or Stage 2 Hypertension) trial was a placebo-controlled, dose-titration study of 12 weeks' duration.[73] A total of 276 patients were randomized to active treatment or placebo. Active treatment started with daily dosing of OM 20 mg. If SeBP was ≥120/80 mm Hg, doses were titrated at 3-week intervals up to a maximum dose of OM/HCTZ 40/25 mg. Statistically significant reductions in mean seated SBP/DBP of –22.3/–12.1 mm Hg from baseline were observed with OM/HCTZ 40/25 mg versus placebo at –0.1/+0.8 mm Hg ($P < 0.0001$).[73] A cumulative BP goal of <140/90 mm Hg at the maximally titrated dose was achieved in 74.1% of patients. In terms of safety, combination OM/HCTZ therapy was well tolerated with higher rates of dizziness at the maximally titrated dose relative to placebo (3.4% vs 0.0%, respectively). Statistical significance was not determined for safety findings in this study.

EFFICACY AND SAFETY OF AMLODIPINE/OLMESARTAN MEDOXOMIL

Amlodipine adds additional BP-lowering ability to olmesartan through the blockade of L-type calcium (Ca^{2+}) channels resulting in vasodilation of blood vessels (see Figure 5).[74] The COACH (Combination of Olmesartan Medoxomil and Amlodipine Besylate in Controlling High Blood Pressure) study was a randomized, double-blind, placebo-controlled, factorial study of 8 weeks' duration where 1940 patients were randomized into OM monotherapy, AML monotherapy, AML/OM combination therapy, or placebo. Statistically significant reductions in SeBP were observed at all combinations of AML/OM versus placebo ($P < 0.001$) (see Figure 6).[75]

Figure 6

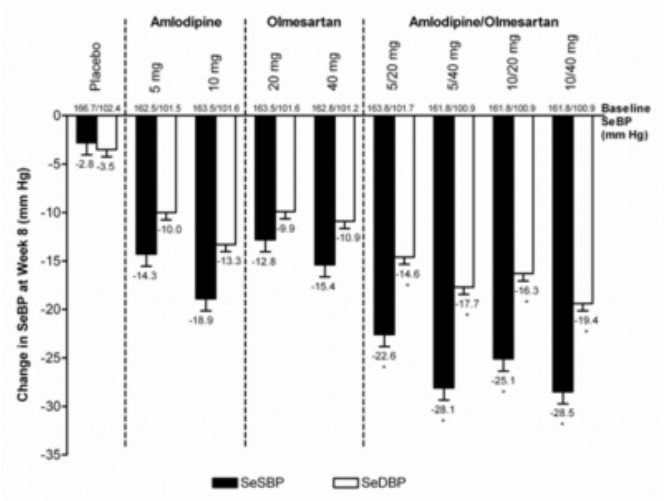
Figure 5. Complementary mechanisms of action (MOA) by which angiotensin II receptor blockers (ARBs) and calcium channel blockers (CCBs) lower blood pressure (BP).



Reprinted from Postgrad Med, 121, Neutel JM, 40-48, Copyright (2009), with permission from JTE Multimedia.[74]

Figure 7

Figure 6. Least-squares mean (standard error) reduction from baseline in seated cuff diastolic blood pressure (SeDBP) and seated cuff systolic blood pressure (SeSBP) after 8 weeks of treatment with olmesartan medoxomil or amlodipine, alone and in combination (last observation carried forward). * < 0.001 vs monotherapy with either component at the same dosage. Adapted from , 30, Chrysant SG, et al, 587-604, Copyright Elsevier (2008). SeBP, seated cuff blood pressure.



After 8 weeks of treatment, 53.2% of patients in the COACH study achieved a goal BP of <140/90 mm Hg (<130/80 mm Hg for patients with diabetes) with combination therapy compared with 32.5% with AML monotherapy and 36.3% with OM monotherapy. Edema, which is a commonly observed adverse effect with AML monotherapy, occurred at a rate of 36.8% in patients treated with AML 10 mg. Combination therapy with AML/OM at a dose of 10/40 mg significantly reduced the incidence of edema to 23.5% (P = 0.0011),[75] lending support to the belief that combination therapy may help decrease or attenuate the adverse effects experienced with monotherapy.

The AZTEC (AZOR Trial Evaluating Blood Pressure Reductions and Control) study assessed reductions in BP with AML/OM combination therapy as determined by ABPM in 185 patients.[76] If SeBP was ≥120/80 mm Hg, AML 5 mg daily was titrated upward every 3 weeks to AML/OM 5/20 mg, AML/OM 5/40 mg, and AML/OM 10/40 mg daily. The primary endpoint in AZTEC was the change from baseline in mean 24-hour ambulatory SBP at week 12. Baseline mean 24-hour ambulatory BP was 144.8/85.7 mm Hg, and a reduction in ambulatory BP of –21.4/–12.7 mm Hg was attained at week 12 (P < 0.0001 vs baseline).[76] A total of 134 of 185 patients required titration to the highest dose of AML/OM 10/40 mg daily. Overall, the AML/OM combination was well tolerated in AZTEC, with only three discontinuations due to adverse events. For the entire treatment period, a total of 14 patients experienced a drug-related TEAE. The most frequently reported TEAE was peripheral edema (2.2%), followed by dizziness (1.1%). A subgroup analysis of the AZTEC study explored the BP-lowering efficacy of AML/OM combination therapy in patients with diabetes and obesity.[77] Similar BP reductions were achieved in the subgroup of patients with diabetes (n = 46). Baseline mean ambulatory BP in this difficult-to-treat subgroup was 145.6/83.1 mm Hg, and a significant reduction from baseline in mean 24-hour ambulatory BP of –21.5/–12.6 mm Hg was attained (P < 0.0001 vs baseline).[77]

EFFICACY AND SAFETY OF OLMESARTAN MEDOXOMIL/AMLODIPINE/HCTZ

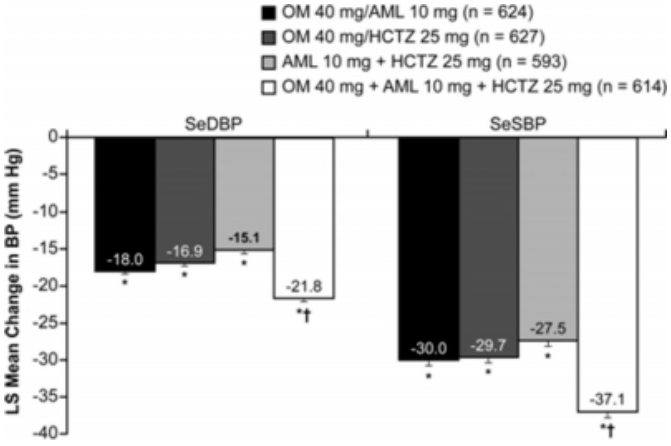
In a 44-week open-label extension of the COACH study, 1684 patients not on combination therapy were started on AML/OM 5/40 mg and then uptitrated to AML/OM 10/40 mg.[78] HCTZ was added on to the maximally titrated AML/OM 10/40 mg dose in increments of 12.5 mg, up to a maximum of HCTZ 25 mg until patients achieved BP goals. At the conclusion of the extension study (week 52), 66.7% of patients achieved goal BP, including patients with diabetes. At the combination dose of OM/AML/HCTZ 40/10/25 mg, a mean change in BP from baseline of –36.1/–19.8 mm Hg was observed compared with a reduction of –29.8/–18.7 mm Hg with the combination dose of OM/AML 40/10 mg. The extension of the COACH study provided more insight into long-term side effects associated with combination therapy. Overall, OM/AML/HCTZ combination therapy was well tolerated. Edema occurred in 10.7% of patients treated with OM/AML/HCTZ 40/10/25 mg compared with 11.1% and 7.0% incidence in patients taking AML/OM 10/40 mg daily and AML/OM 5/40 mg daily, respectively.[78]

TRINITY (Triple Therapy with Olmesartan Medoxomil, Amlodipine, and Hydrochlorothiazide in Hypertensive Patients Study) lends some insight into the potent BP reductions afforded by triple combination therapy.[79] TRINITY, a phase III, multicenter, parallel-group study of 12 weeks' duration in 2492 patients, compared the efficacy and tolerability of OM/AML/HCTZ 40/10/25 mg with

corresponding doses of AML/OM, OM/HCTZ, and AML/HCTZ combination therapy. The least-squares mean reduction in BP was –37.1/–21.8 mm Hg for the OM/AML/HCTZ group compared with –27.5 to –30.0/–15.1 to –18.0 mm Hg for the other three treatment groups, a statistically significant reduction relative to the other treatment groups ($P < 0.0001$) (see Figure 7).[79] A total of 69.9% of patients achieved a BP goal of <140/90 mm Hg on OM/AML/HCTZ combination therapy compared with the other three treatment groups, which ranged from 41.1%–53.4% ($P < 0.0001$).[79] Adverse events were found to be mild to moderate in severity, with no statistically significant differences observed between treatment groups.

Figure 8

Figure 7. Least-squares (LS) mean (standard error) change from baseline in seated cuff diastolic BP (SeDBP) and seated cuff systolic BP (SeSBP) after 12 weeks of treatment with dual or triple combination treatment. * < 0.001 vs baseline; P < 0.001 vs each dual combination treatment. Reprinted by permission from Macmillan Publishers Ltd: , Oparil S, et al, 24(12):831-838, copyright (2010). AML, amlodipine; BP, blood pressure; HCTZ, hydrochlorothiazide; OM, olmesartan medoxomil.



The BP-CRUSH (Blood Pressure Control in All Subgroups with Hypertension) study investigated the efficacy of AML/OM combination therapy in patients with hypertension uncontrolled on monotherapy to reach JNC 7 BP goals.[80] A total of 999 patients were switched from previously failed monotherapy to a fixed-dose combination of AML/OM 5/20 mg. At 4-week intervals, therapy was up-titrated to AML/OM 5/40 mg and AML/OM 10/40 mg if mean SBP was ≥120 mm Hg or if mean DBP was ≥70 mm Hg. Patients were up-titrated to AML/OM 10/40 mg + HCTZ 12.5 mg and AML/OM 10/40 mg + HCTZ 25 mg if mean SBP was ≥125 mm Hg or if mean DBP was ≥75 mm Hg. By week 12, 77.1% of patients achieved a cumulative SeBP goal of <140/90 mm Hg (<130/80 mm Hg for patients with type 2 diabetes), with the proportion increasing to 90.3% at week 20 at the maximally titrated dose of AML/OM 10/40 mg + HCTZ 25 mg. The mean end-of-study SeBP at week 20 was 129.6/79.7 mm Hg, a decrease of –25.1/–13.7 mm Hg from a baseline mean SeBP of 154.7/93.4 mm Hg. BP reductions across all titration steps were statistically significant versus baseline ($P < 0.0001$).[80]

BEYOND BLOOD PRESSURE EFFECTS OF OLMESARTAN MEDOXOMIL

Recent evidence suggests the benefits of olmesartan are not limited to its antihypertensive mechanism of action. The OLAS (Olmesartan/Amlodipine vs Olmesartan/Hydrochlorothiazide in Metabolic Syndrome) study was conducted to investigate the effects of OM-based combination therapy on inflammatory and metabolic parameters in 120 non-diabetic patients with metabolic syndrome.[81] Following a placebo washout period, patients were randomized to either OM/AML or OM/HCTZ with doses titrated upwards every 13 weeks to maximal combination doses. Once at maximized combination therapy (week 26), doxazosin was added-on, starting at 4 mg and up-titrated to 8 mg at week 39, so long as SBP was ≥140 mm Hg. After 78 weeks of treatment, both treatment arms demonstrated similar significant reductions in albuminuria from baseline ($P < 0.01$), while the OM/AML treatment group significantly reduced the insulin resistance index ($P < 0.01$).[81] In terms of inflammatory markers, only C-reactive protein (CRP) was reduced significantly in both treatment arms ($P < 0.05$).[81] Otherwise, only the OM/AML treatment group significantly reduced tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, IL-6, IL-8, intercellular adhesion molecule-1, and vascular cell adhesion molecule-1.[81]

Apart from inflammatory mediators and metabolic indicators, great interest and research is focused on the effects of olmesartan on biomarkers that are indicative of cardiovascular health. The OLIVUS (Impact of Olmesartan on Progression of Coronary Atherosclerosis: Evaluation by Intravascular Ultrasound) trial looked at the effects of olmesartan on the progression of atherosclerosis as evaluated by intravascular ultrasound (IVUS) in patients with stable angina pectoris.[82] In total, 247 patients were enrolled and randomized to OM treatment or control groups. Following percutaneous coronary intervention, IVUS was performed in nonculprit vessels to obtain baseline atheroma volume.

Following 12–16 months of treatment, IVUS was performed again to detect changes in atheroma volume. At the end of the study, total atheroma volume increased by 5.4% in the control group compared with a significantly lower increase of 0.6% for OM ($P < 0.05$).[82] The percent change in atheroma volume was 3.1% for control and –0.7% for OM ($P < 0.05$).[82] The investigators concluded that OM may have played a role in slowing the rate of progression of coronary atheroma.

The EUTOPIA study investigated the anti-inflammatory effects of OM alone and in combination with the HMG-CoA reductase inhibitor pravastatin in patients with hypertension and microinflammation.[83] Patients were treated for 12 weeks with OM (n = 100) or placebo (n = 99), and pravastatin was added at week 6 for all patients. HCTZ was added, as necessary, to control BP. In the OM group, high-sensitivity CRP (–15.1%; $P < 0.05$), high-sensitivity TNF-α (–8.9%; $P < 0.02$), IL-6 (–14.0%; $P < 0.05$), and monocyte chemotactic protein-1 (–6.5%; $P < 0.01$) were significantly reduced after 6 weeks of therapy.[83] Placebo treatment had no major effects on these markers. The combination of pravastatin and OM further reduced levels of high-sensitivity CRP (–21.1%; $P < 0.02$), high-sensitivity TNF-α (–13.6%; $P < 0.01$), and IL-6 (–18.0%; $P < 0.01$) at week 12, but pravastatin alone did not significantly alter inflammation markers.

CONCLUSIONS

Hypertension is a prevalent condition that requires attentive and comprehensive management of patients to reduce cardiovascular morbidity and mortality. Nurse practitioners can positively impact patient outcomes by educating patients, encouraging positive lifestyle changes, and incorporating combination drug therapy in the treatment of hypertension where appropriate. Olmesartan medoxomil and its family of fixed-dose combination therapies treat a wide variety of patient populations who cannot obtain BP control on monotherapy. Fixed-dose combination therapies can increase adherence and minimize side effects experienced from taking multiple antihypertensive agents versus taking them as high-dose monotherapy. A large body of evidence suggests fixed-dose combination therapy allows for safe achievement of BP control in difficult-to-treat populations.

ACKNOWLEDGEMENTS

Robert Schupp, PharmD, and Christopher J. Jones, PhD, of inScience Communications provided editorial support, which was funded by Daiichi Sankyo, Inc.

Funding Source: The preparation of this manuscript was supported by Daiichi Sankyo, Inc.

References

1. Egan BM, Zhao Y, Axon RN. US trends in prevalence, awareness, treatment, and control of hypertension, 1988–2008. JAMA. 2010;303(20):2043-2050.
2. Ostchega Y, Yoon SS, Hughes J, Louis T. Hypertension awareness, treatment, and control–continued disparities in adults: United States, 2005–2006. NCHS Data Brief. 2008(3):1-8.
3. Qureshi AI, Suri MF, Kirmani JF, Divani AA. Prevalence and trends of prehypertension and hypertension in United States: National Health and Nutrition Examination Surveys 1976 to 2000. Med Sci Monit. 2005;11(9):CR403-409.
4. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003;42(6):1206-1252.
5. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360(9349):1903-1913.
6. Thrift AG, McNeil JJ, Forbes A, Donnan GA. Risk factors for cerebral hemorrhage in the era of well-controlled hypertension. Melbourne Risk Factor Study (MERFS) Group. Stroke. 1996;27(11):2020-2025.
7. Coresh J, Wei GL, McQuillan G, et al. Prevalence of high blood pressure and elevated serum creatinine level in the United States: findings from the third National Health and Nutrition Examination Survey (1988–1994). Arch Intern Med. 2001;161(9):1207-1216.
8. Hsu CY, McCulloch CE, Darbinian J, Go AS, Iribarren C. Elevated blood pressure and risk of end-stage renal disease in subjects without baseline kidney disease. Arch Intern Med. 2005;165(8):923-928.
9. Bakris GL, Williams M, Dworkin L, et al. Preserving renal function in adults with hypertension and diabetes: a consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. Am J Kidney Dis. 2000;36(3):646-661.
10. Roberts ME, Epstein BJ. Optimizing management of hypertension with combination therapy: considerations for the nurse practitioner. J Cardiovasc Nurs. 2009;24(5):380-389.
11. DiMatteo MR, Giordani PJ, Lepper HS, Croghan TW. Patient adherence and medical treatment outcomes: a meta-analysis. Med Care. 2002;40(9):794-811.
12. Ho PM, Spertus JA, Masoudi FA, et al. Impact of medication therapy discontinuation on mortality after myocardial infarction. Arch Intern Med. 2006;166(17):1842-1847.
13. Jackevicius CA, Mamdani M, Tu JV. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. JAMA. 2002;288(4):462-467.
14. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. 2005;353(5):487-497.
15. Feldman RD, Zou GY, Vandervoort MK, Wong CJ, Nelson SA, Feagan BG. A simplified approach to the treatment of uncomplicated hypertension: a cluster randomized, controlled trial. Hypertension. 2009;53(4):646-653.
16. He J, Whelton PK, Appel LJ, Charleston J, Klag MJ. Long-term effects of weight loss and dietary sodium reduction on incidence of hypertension. Hypertension.

2000;35(2):544-549.
17. Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. N Engl J Med. 2001;344(1):3-10.
18. Xin X, He J, Frontini MG, Ogden LG, Motsamai OI, Whelton PK. Effects of alcohol reduction on blood pressure: a meta-analysis of randomized controlled trials. Hypertension. 2001;38(5):1112-1117.
19. Kelley GA, Kelley KS. Progressive resistance exercise and resting blood pressure: A meta-analysis of randomized controlled trials. Hypertension. 2000;35(3):838-843.
20. Turnbull F. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. Lancet. 2003;362(9395):1527-1535.
21. Pitt B, Reichek N, Willenbrock R, et al. Effects of eplerenone, enalapril, and eplerenone/enalapril in patients with essential hypertension and left ventricular hypertrophy: the 4E-left ventricular hypertrophy study. Circulation. 2003;108(15):1831-1838.
22. Mancia G, Laurent S, Agabiti-Rosei E, et al. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. J Hypertens. 2009;27(11):2121-2158.
23. American Diabetes Association. Standards of medical care in diabetes–2012. Diabetes Care. 2012;35 Suppl 1:S11-S63.
24. Pickering TG, Hall JE, Appel LJ, et al. Recommendations for blood pressure measurement in humans and experimental animals: part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. Hypertension. 2005;45(1):142-161.
25. Kario K, Pickering TG, Umeda Y, et al. Morning surge in blood pressure as a predictor of silent and clinical cerebrovascular disease in elderly hypertensives: a prospective study. Circulation. 2003;107(10):1401-1406.
26. Franklin SS, Gustin Wt, Wong ND, et al. Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. Circulation. 1997;96(1):308-315.
27. National Institute for Clinical Excellence. Hypertension: clinical management of primary hypertension in adults, NICE clinical guideline 127, August 2011. http://www.nice.org.uk/nicemedia/live/13561/56008/56008.pdf. Accessed January 27, 2012.
28. Pickering TG, Miller NH, Ogedegbe G, Krakoff LR, Artinian NT, Goff D. Call to action on use and reimbursement for home blood pressure monitoring: a joint scientific statement from the American Heart Association, American Society of Hypertension, and Preventive Cardiovascular Nurses Association. Hypertension. 2008;52(1):10-29.
29. Douglas JG, Bakris GL, Epstein M, et al. Management of high blood pressure in African Americans: consensus statement of the Hypertension in African Americans Working Group of the International Society on Hypertension in Blacks. Arch Intern Med. 2003;163(5):525-541.
30. Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics–2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation. 2009;119(3):480-486.
31. Williams B, Lacy PS. Central aortic pressure and clinical outcomes. J Hypertens. 2009;27(6):1123-1125.
32. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. Lancet. 2005;365(9455):217-223.
33. Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. N Engl J Med. 2008;358(18):1887-1898.
34. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). JAMA. 1991;265(24):3255-3264.
35. Muller JE, Tofler GH, Stone PH. Circadian variation and triggers of onset of acute cardiovascular disease. Circulation. 1989;79(4):733-743.
36. Aronow WS, Fleg JL, Pepine CJ, et al. ACCF/AHA 2011 Expert Consensus Document on Hypertension in the Elderly: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. Circulation. 2011;123(21):2434-2506.
37. Wong ND, Lopez VA, L'Italien G, Chen R, Kline SE, Franklin SS. Inadequate control of hypertension in US adults with cardiovascular disease comorbidities in 2003–2004. Arch Intern Med. 2007;167(22):2431-2436.
38. Barnett AH, Bain SC, Bouter P, et al. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. N Engl J Med. 2004;351(19):1952-1961.
39. Cooper-DeHoff RM, Gong Y, Handberg EM, et al. Tight blood pressure control and cardiovascular outcomes among hypertensive patients with diabetes and coronary artery disease. JAMA. 2010;304(1):61-68.
40. Cushman WC, Evans GW, Byington RP, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med. 2010;362(17):1575-1585.
41. Bangalore S, Kumar S, Lobach I, Messerli FH. Blood pressure targets in subjects with type 2 diabetes mellitus/impaired fasting glucose: observations from traditional and bayesian random-effects meta-analyses of randomized trials. Circulation. 2011;123(24):2799-2810.
42. Flack JM, Sica DA, Bakris G, et al. Management of high blood pressure in blacks. An Update of the International Society on Hypertension in Blacks Consensus Statement. Hypertension. 2010;56:780-800.
43. Levine RS, Foster JE, Fullilove RE, et al. Black-white inequalities in mortality and life expectancy, 1933–1999: implications for healthy people 2010. Public Health Rep. 2001;116(5):474-483.
44. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation. 2005;112(17):2735-2752.
45. Israili ZH, Lyoussi B, Hernandez-Hernandez R, Velasco M. Metabolic syndrome: treatment of hypertensive patients. Am J Ther. 2007;14(4):386-402.
46. Abuissa H, Jones PG, Marso SP, O'Keefe JH, Jr. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for prevention of type 2 diabetes: a meta-analysis of randomized clinical trials. J Am Coll Cardiol. 2005;46(5):821-826.
47. Cushman WC, Ford CE, Cutler JA, et al. Success and predictors of blood pressure control in diverse North American settings: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). J Clin Hypertens (Greenwich). 2002;4(6):393-404.
48. Dahlof B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study

(LIFE): a randomised trial against atenolol. Lancet. 2002;359(9311):995-1003.
49. Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med. 2008;359(23):2417-2428.
50. Benicar (olmesartan medoxomil) tablet, film coated: US Prescribing Information. Parsippany, NJ: Daiichi Sankyo, Inc.; 2012.
51. Diovan (valsartan) tablet: US Prescribing Information. East Hanover, NJ: Novartis Pharmaceuticals Corp.; 2012.
52. Cozaar (losartan potassium) tablet, film coated: US Prescribing Information. Whitehouse Station, NJ: Merck Sharp & Dohme Corp.; 2011.
53. Edarbyclor (azilsartan medoxomil and chlorthalidone) tablet: US Prescribing Information. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; 2011.
54. Atacand HCT (candesartan cilexitil and hydrochlorothiazide) tablet: US Prescribing Information. Wilmington, DE: AstraZeneca; 2011.
55. Teveten HCT (eprosartan mesylate and hydrochlorothiazide) tablet: US Prescribing Information. North Chicago, IL: Abbott Laboratories; 2011.
56. Avalide (irbesartan and hydrochlorothiazide) tablet, film coated: US Prescribing Information. Princeton, NJ: Bristol-Myers Squibb; 2012.
57. Hyzaar (losartan potassium and hydrochlorothiazide) tablet, film coated: US Prescribing Information. Whitehouse Station, NJ: Merck Sharp & Dohme Corp.; 2011.
58. Benicar HCT (olmesartan medoxomil-hydrochlorothiazide) tablet, film coated: US Prescribing Information. Parsippany, NJ: Daiichi Sankyo, Inc.; 2012.
59. Azor (amlodipine besylate and olmesartan medoxomil) tablet, film coated: US Prescribing Information. Parsippany, NJ: Daiichi Sankyo, Inc.; 2012.
60. Tribenzor (olmesartan medoxomil/amlodipine besylate/hydrochlorothiazide) tablet, film coated: US Prescribing Information. Parsippany, NJ: Daiichi Sankyo, Inc.; 2010.
61. Micardis HCT (telmisartan and hydrochlorothiazide) tablet: US Prescribing Information. Ridgefield, CT: Boehringer Ingelheim; 2012.
62. Twynsta (telmisartan/amlodipine) tablet, multilayer: US Prescribing Information. Deerfield, CT: Boehringer Ingelheim; 2009.
63. Diovan HCT (valsartan and hydrochlorothiazide) tablet, film coated: US Prescribing Information. East Hanover, NJ: Novartis Pharmaceuticals; 2012.
64. Exforge (amlodipine besylate and valsartan), film coated: US Prescribing Information. East Hanover, NJ: Novartis Pharmaceuticals; 2012.
65. Exforge HCT (amlodipine valsartan and hydrochlorothiazide) tablet, film coated: US Prescribing Information. East Hanover, NJ: Novartis Pharmaceuticals; 2012.
66. Valturna (aliskiren hemifumarate and valsartan) tablet, film coated: US Prescribing Information. East Hanover, NJ: Novartis Pharmaceuticals; 2012.
67. Mire DE, Silfani TN, Pugsley MK. A review of the structural and functional features of olmesartan medoxomil, an angiotensin receptor blocker. J Cardiovasc Pharmacol. 2005;46(5):585-593.
68. Dicpinigaitis PV. Angiotensin-converting enzyme inhibitor-induced cough: ACCP evidence-based clinical practice guidelines. Chest. 2006;129(1 Suppl):169S-173S.
69. Lotensin (benazepril hydrochloride) tablet: US Prescribing Information. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2012.
70. Chrysant SG, Weber MA, Wang AC, Hinman DJ. Evaluation of antihypertensive therapy with the combination of olmesartan medoxomil and hydrochlorothiazide. Am J Hypertens. 2004;17(3):252-259.
71. Kereiakes DJ, Neutel J, Stoakes KA, et al. The effects of an olmesartan medoxomil-based treatment algorithm on 24-hour blood pressure levels in elderly patients aged 65 and older. J Clin Hypertens. 2009;11(8):411-421.
72. Neutel JM, Kereiakes DJ, Waverczak WF, Stoakes KA, Xu J, Shojaee A. Effects of an olmesartan medoxomil based treatment algorithm on 24-hour blood pressure control in patients with hypertension and type 2 diabetes. Curr Med Res Opin. 2010;26(3):721-728.
73. Oparil S, Chrysant SG, Kereiakes D, et al. Results of an olmesartan medoxomil-based treatment regimen in hypertensive patients. J Clin Hypertens (Greenwich). 2008;10(12):911-921.
74. Neutel JM. Complementary mechanisms of angiotensin receptor blockers and calcium channel blockers in managing hypertension. Postgrad Med. 2009;121(2):40-48.
75. 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(4):587-604.
76. Punzi H, Neutel JM, Kereiakes DJ, et al. Efficacy of amlodipine and olmesartan medoxomil in patients with hypertension: the AZOR Trial Evaluating Blood Pressure Reductions and Control (AZTEC) study. Ther Adv Cardiovasc Dis. 2010;4(4):209-221.
77. Punzi H, Shojaee A, Waverczak WF, Maa JF. Efficacy of amlodipine and olmesartan medoxomil in hypertensive patients with diabetes and obesity. J Clin Hypertens (Greenwich). 2011;13(6):422-430.
78. Chrysant SG, Oparil S, Melino M, Karki S, Lee J, Heyrman R. Efficacy and safety of long-term treatment with the combination of amlodipine besylate and olmesartan medoxomil in patients with hypertension. J Clin Hypertens (Greenwich). 2009;11(9):475-482.
79. 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(7):1252-1269.
80. Weir MR, Hsueh WA, Nesbitt SD, et al. A titrate-to-goal study of switching patients uncontrolled on antihypertensive monotherapy to fixed-dose combinations of amlodipine and olmesartan medoxomil +/- hydrochlorothiazide. J Clin Hypertens (Greenwich). 2011;13(6):404-412.
81. Martinez-Martin FJ, Rodriguez-Rosas H, Peiro-Martinez I, Soriano-Perera P, Pedrianes-Martin P, Comi-Diaz C. Olmesartan/amlodipine vs olmesartan/hydrochlorothiazide in hypertensive patients with metabolic syndrome: the OLAS study. J Hum Hypertens. 2011;25(6):346-353.
82. Hirohata A, Yamamoto K, Miyoshi T, et al. Impact of olmesartan on progression of coronary atherosclerosis a serial volumetric intravascular ultrasound analysis from the OLIVUS (impact of OLmesarten on progression of coronary atherosclerosis: evaluation by intravascular ultrasound) trial. J Am Coll Cardiol. 2010;55(10):976-982.
83. Fliser D, Buchholz K, Haller H. Antiinflammatory effects of angiotensin II subtype 1 receptor blockade in hypertensive patients with microinflammation. Circulation. 2004;110(9):1103-1107.

Author Information

Mary Ellen E. Roberts, DNP, RN, APN-C, FAANP
Cardiology Nurse Practitioner