



Angiotensin Modulator Combinations

Therapeutic Class Review (TCR)

July 29, 2014

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
amlodipine / aliskiren (Tekamlo™) ¹	Novartis	Treatment of hypertension
amlodipine / aliskiren / HCTZ (Amturnide™) ²	Novartis	Hypertension (not as initial therapy)
amlodipine / benazepril (Lotrel®) ³	generic	Hypertension (not as initial therapy)
amlodipine / olmesartan (Azor™) ⁴	Daiichi Sankyo	Treatment of hypertension either alone or in combination with other agents Initial therapy in patients likely to need multiple antihypertensive agents to achieve their blood pressure goals
amlodipine / olmesartan / HCTZ (Tribenzor™) ⁵	Daiichi Sankyo	Hypertension (not as initial therapy)
amlodipine / telmisartan (Twynsta®) ⁶	generic, Boehringer Ingelheim	Treatment of hypertension alone or in combination with other agents Initial treatment of hypertension in patients who will likely require multiple medications for blood pressure control
amlodipine / valsartan (Exforge®) ⁷	Novartis	Initial treatment of hypertension in patients who will likely require multiple medications for blood pressure control Treatment of hypertension for patients not adequately controlled on monotherapy
amlodipine / valsartan / hydrochlorothiazide (HCTZ) (Exforge HCT®) ⁸	Novartis	Hypertension (not initial therapy)
verapamil SR / trandolapril (Tarka®) ⁹	generic, Abbott	Hypertension (not as initial therapy)

* Valturna –valsartan, aliskiren fixed dose tablets were discontinued by Novartis in 2012.¹⁰

OVERVIEW

The Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 8) treatment algorithm for hypertension includes combination therapy as a therapeutic option.¹¹ Most hypertensive patients require at least two medications to achieve adequate blood pressure (BP) reduction as seen in a large clinical trial.¹²

PHARMACOLOGY

These agents are a fixed-dose combination of two or three of the following: an angiotensin II receptor blocker (ARB) or an ACE inhibitor in combination with a calcium channel blocker (CCB), with or without the addition of a thiazide diuretic, and a direct renin inhibitor (DRI). ACE inhibitors included in this class of combination products include benazepril (Lotensin[®]) and trandolapril (Mavik[®]).

Aliskiren (Tekturna[®]) is a renin inhibitor which targets the renin-angiotensin-aldosterone system (RAAS) at the point of activation by inhibiting renin and blocking conversion of angiotensinogen to angiotensin I, thereby decreasing plasma renin activity (PRA).¹³

ACE inhibitors prevent the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor, by competing with angiotensin I for the active site of ACE. The reduction of angiotensin II formation decreases vasoconstriction, decreases aldosterone secretion, and increases plasma renin. This causes a reduction in blood pressure and total peripheral resistance, and decreased sodium and water retention.¹⁴ There is also a possible local action within the vascular wall that is responsible for blood pressure reduction.¹⁵

Olmesartan (Benicar[®]), telmisartan (Micardis[®]), and valsartan (Diovan[®]) are angiotensin II receptor blockers. Angiotensin II causes vasoconstriction, release of aldosterone and antidiuretic hormone, sympathetic activation, and constriction of the efferent arterioles of the glomerulus in the kidneys.^{16,17} ARBs block the vasoconstrictive and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor found in many tissues such as vascular smooth muscle and the adrenal gland. Non-ACE pathways also produce angiotensin II. ARBs do not inhibit ACE (kinase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin), nor do they bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Calcium channel blockers inhibit calcium ions from moving across the cell membrane. The limitation of calcium entering into the cells causes a decrease in mechanical contraction of myocardial and smooth muscle, thereby causing dilation of systemic arteries and a decrease in total peripheral resistance, systemic blood pressure, and the afterload of the heart. The dihydropyridine CCB amlodipine (Norvasc[®]) is a potent vasodilator and can increase or have a neutral effect on vascular permeability.¹⁸ The nondihydropyridine CCB verapamil is a potent vasodilator, but verapamil has a greater depressive effect on cardiac conduction and contractility.

Hydrochlorothiazide is a thiazide diuretic that exhibits its pharmacological effects by blocking the reabsorption of sodium and chloride leading to diuresis and a reduction in intravascular volume. Concurrent administration of an angiotensin II receptor antagonist, such as valsartan, and a thiazide diuretic may help to decrease potassium loss that occurs with thiazide diuretic therapy.^{19,20}

Blood pressure is lowered through the antihypertensive mechanisms of all components of the combinations.

PHARMACOKINETICS

There are no pharmacokinetic profile changes with combination products versus each single agent, except with verapamil SR 240 mg and trandolapril 4 mg (Tarka), in which an increase in AUC and Cmax are seen with verapamil.²¹

Brand Name	Generic Name	Bioavailability (%)	Half-Life (hr)	Metabolites	Excretion (%)
Tekamlo ^{22,23}	amlodipine	64-90	30-50	extensively metabolized	Urine: 70
	aliskiren	~2.5	~ 40	metabolized	Urine: ~25
Amturnide ^{24,25}	amlodipine	64-90	30-50	extensively metabolized	Urine: 70
	aliskiren	~2.5	~ 40	metabolized	Urine: ~25
	hydrochlorothiazide	--	5.8-18.9	not metabolized	Urine: 61
Lotrel ²⁶	amlodipine	64-90	~ 48	extensively metabolized	Urine: 70
	benazepril	> 37	10-11	benazeprilat (~ 100%)	Primarily urine
Azor ²⁷	amlodipine	64-90	30-50	extensively metabolized	Urine: 70
	olmesartan	26	13	none significant	Feces: 50-65 Urine: 35-50
Tribenzor ²⁸	amlodipine	64-90	30-50	extensively metabolized	Urine: 55
	olmesartan	26	13	none significant	Feces: 50-65 Urine: 35-50
	hydrochlorothiazide	--	5.6-14.8	not metabolized	Urine: 61
Twynsta ²⁹	amlodipine	64-90	30-50	extensively metabolized	Urine: 70
	telmisartan	42-58	24	metabolized to glucuronide conjugate	Feces: > 97
Exforge ³⁰	amlodipine	64-90	30-50	extensively metabolized	Urine: 70
	valsartan	25	6	20% of dose converted to metabolites	Urine: 13 Feces: 83
Exforge HCT ^{31,32}	amlodipine	64-90	30-50	extensively metabolized	Urine: 70
	hydrochlorothiazide	--	5.8-18.9	not metabolized	Urine: 61
	valsartan	10-35	6	20% of dose converted to metabolites	Urine: 13 Feces: 83
Tarka ³³	trandolapril	10 (as trandolapril)	10	trandolaprilat	Urine: 33 Feces: 66
	verapamil SR	20-35	6-11	12 metabolites, norverapamil is 20% as potent as parent	Urine: 70 Feces: 16

CONTRAINDICATIONS/WARNINGS^{34,35,36,37,38,39, 40,41,42}

Aliskiren and aliskiren containing products are contraindicated with angiotensin II receptor blockers (ARBs), or angiotensin converting enzyme inhibitors (ACEIs), in patients with diabetes due to increased risk of renal impairment, hyperkalemia, and hypotension.

All product labeling for agents in this review contain boxed warning regarding the use of drugs that act directly on the renin-angiotensin-aldosterone system during pregnancy can cause fetal and neonatal morbidity and death and when pregnancy is detected, should be discontinued as soon as possible.

Angioedema of the head and neck can occur with any angiotensin modulating agent. If angioedema involves the tongue or airway, respiratory distress may occur and could result in death without prompt treatment. Angioedema of the face, extremities, lips, tongue, glottis and/or larynx associated with aliskiren use has occurred in patients without prior history of angioedema with ACE inhibitors or ARBs, and may occur at anytime during therapy. Immediate permanent discontinuation of aliskiren is advised if angioedema involves the throat, tongue, glottis or larynx. Verapamil SR/trandolapril (Tarka) is contraindicated in patients with a history of angioedema related to previous ACE Inhibitor therapy. Amlodipine/benazepril (Lotrel) use is contraindicated in patients with a history of angioedema regardless of previous ACE Inhibitor use.

Hypersensitivity to any of these products is considered a contraindication.

Caution should be exercised when using aliskiren in patients with an activated renin-angiotensin system, such as volume and/or salt-depleted patients including patients on high doses of diuretics, as symptomatic hypotension may occur with initiation of treatment with aliskiren.

Serum potassium should be monitored periodically in patients receiving aliskiren as drugs that affect the renin-angiotensin system can cause hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes, combination use with ARBs or ACEI, non-steroidal anti-inflammatory drugs (NSAIDs), or potassium supplements or potassium sparing diuretics. Avoid use of these agents in patients with hyperkalemia.

Renal function should be monitored periodically. Changes in renal function, including acute renal failure, can be caused by drugs that affect the renin-angiotensin system. Patients whose renal function may depend in part on the activity of the renin-angiotensin system (e.g., patients with renal artery stenosis, severe heart failure, post-myocardial infarction or volume depletion) or patients receiving ARBs, ACEIs or NSAIDs therapy may be at particular risk for developing acute renal failure on aliskiren. Concomitant use of aliskiren with an ARB or ACEI is not recommended in patients with moderate renal impairment (GFR <60 mL/min). In patients who develop a clinically significant decrease in renal function withholding or discontinuing therapy should be considered.

Severe cutaneous adverse reactions (e.g. Stevens Johnson syndrome and toxic epidermal necrolysis) have occurred with aliskiren.

In both the Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) and Olmesartan Reducing Incidence of End Stage Renal Disease in Diabetic Nephropathy Trial (ORIENT) trials, patients with type 2 diabetes were given either olmesartan or placebo to determine if treatment with olmesartan would slow the progression of kidney disease. An unexpected finding observed in both trials was a greater number of deaths from a cardiovascular cause (MI, sudden death, or stroke) in the olmesartan-treated patients compared to placebo. The FDA has completed its safety review in

which patients with type 2 diabetes were taking olmesartan (Benicar) and found no clear evidence of a higher rate of cardiovascular risk as compared to placebo.⁴³ The FDA reminds practitioners that numerous clinical trials with olmesartan as well as trials with other ARBs have not suggested an increased risk of cardiovascular-related death. Currently, the FDA still believes that the benefits of olmesartan in patients with hypertension continue to outweigh the potential risks.

Sprue-like enteropathy has been reported in patients taking olmesartan months to years after the start of the drug.^{44,45} Severe, chronic diarrhea with substantial weight loss has been reported and if a patient develops these symptoms while on olmesartan other etiologies must be excluded. Stopping therapy of olmesartan in cases where no other etiologies are identified should be considered.

In July 2010, the FDA announced that they were conducting a review of ARBs after a meta-analysis including data from over 60,000 patients suggested that ARBs may be associated with a small increased risk of cancer.⁴⁶ In June 2011, the FDA concluded that treatment with an ARB does not increase cancer risk.⁴⁷ To draw this conclusion, FDA conducted a trial-level meta-analysis of 31 clinical trial in which patients were randomized to treatment with an ARB (n=84,461) or a non-ARB (n=71,355). The meta-analysis evaluated the association between ARBs and the risk of incident (new) cancer, cancer-related death, breast cancer, lung cancer and prostate cancer. The rate of cancer events in the ARB group was 1.82 per 100 patient-years compared to 1.84 per 100 patient-years in non-ARB comparators. The relative risk of cancer in patients taking ARBs was 0.99 (95% confidence interval, 0.92 to 1.06). FDA also found no evidence of association between ARBs and cancer-related death (relative risk 1.04, 95% CI, 0.96 to 1.13), breast cancer (odds ratio 1.06, 95% CI, 0.90 to 1.23), lung cancer (odds ratio 1.07, 95% CI, 0.89 to 1.29), or prostate cancer (odds ratio 1.05, 95% CI, 0.95 to 1.17).

Another meta-analysis assessed the association between antihypertensive drugs and cancer risk.⁴⁸ It included 70 randomized controlled trials with 324,168 participants and recorded no difference in the risk of cancer with ARBs. There was an increased risk with the combination of ACE Inhibitors plus ARBs (2.3%, 1.14, 95% CI, 1.02-1.28); however, this risk was not apparent in the random-effects model (odds ratio 1.15, 95% CI, 0.92-1.38).

Due to the verapamil component, verapamil SR/trandolapril (Tarka) is contraindicated in patients with severe left ventricular dysfunction (LVD), hypotension (SBP < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (except in patients with a functioning artificial ventricular pacemaker), second or third degree AV block (except in patients with a functioning artificial ventricular pacemaker), atrial flutter or atrial fibrillation and an accessory bypass tract (e.g. Wolff-Parkinson-White, Lown-Ganong-Levine syndromes).

Amlodipine/aliskiren/HCTZ (Amturnide), amlodipine/valsartan/HCTZ (Exforge HCT) and amlodipine/olmesartan/HCTZ (Tribenzor) are contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs due to the HCTZ component. Thiazide diuretics may also cause exacerbation or activation of systemic lupus erythematosus. The potential exists for electrolyte (e.g., hypercalcemia, hypochloremic alkalosis, hypokalemia, hypomagnesemia, hyponatremia, and hyperuricemia) or fluid imbalances; monitoring is recommended.

Hydrochlorothiazide can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms such as acute onset of decreased visual acuity or ocular pain can occur within hours to weeks of drug initiation. If untreated, acute angle-closure glaucoma can lead to permanent vision loss. Hydrochlorothiazide should be discontinued as rapidly as possible. Prompt medical or surgical treatments may be considered if the intraocular pressure remains uncontrolled.

Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Worsening angina and acute myocardial infarction may develop after beginning or increasing the dose of amlodipine, especially in patients with severe obstructive coronary artery disease.

Appropriate caution is necessary when using amlodipine in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

DRUG INTERACTIONS^{49,50,51,52,53,54, 55,56,57}

ACE inhibitors interact with azathioprine, cyclosporine, lithium, nonsteroidal anti-inflammatory drugs (NSAIDs), potassium sparing diuretics, trimethoprim, and eplerenone (Inspra[®]). Concurrent use of loop and thiazide diuretics can increase the risk of hypovolemia and increase the risk of nephrotoxicity.

Increases in serum lithium concentrations and lithium toxicity have been reported with concurrent use of lithium and ARBs. Serum lithium levels should be monitored with concurrent use. Verapamil can interact with digoxin, lithium, erythromycin, clarithromycin, beta-blockers, carbamazepine, rifampin, phenobarbital, cyclosporine, theophylline, and select antiarrhythmic agents.

In elderly volume-depleted (including those on diuretic therapy), or renally compromised patients, coadministration of NSAIDs, including selective COX-2 inhibitors, with agents acting on the renin-angiotensin system (ACE inhibitors, ARBs, aliskiren) may result in decreased renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving and NSAID therapy. In addition, the antihypertensive effect of ACE inhibitors, ARBs, and aliskiren may be reduced by NSAIDs including selective COX-2 inhibitors.

Coadministration of multiple doses of amlodipine or verapamil with 80 mg simvastatin may result in a significant increase in exposure to simvastatin. Simvastatin dose should not exceed 20 mg per day in patients on amlodipine. For patients on verapamil, limit the dose of simvastatin to 10 mg daily and the dose of lovastatin to 40 mg. Lower starting and maintenance doses of other CYP3A4 substrates (e.g., atorvastatin) may be required as verapamil may increase the plasma concentration of these drugs.

Hydrochlorothiazide may potentiate the orthostatic effects of alcohol, barbiturates or narcotics; interact with oral antidiabetic drugs and insulin requiring a dose adjustment of the antidiabetic agent; anionic exchange resins (such as cholestyramine) impair the absorption of HCTZ; electrolyte depletion is intensified with corticosteroids; lithium clearance is reduced; non-steroidal anti-inflammatory drugs (NSAIDs) can reduce diuretic, natriuretic and antihypertensive effects of diuretics; and symptomatic hyponatremia may be seen with carbamazepine.

Concomitant use of aliskiren and cyclosporine or itraconazole is not recommended as the blood concentrations of aliskiren may be significantly increased.

No drug interaction studies have been conducted with Amturnide, or Tekamlo and other drugs, although studies with the individual components, aliskiren and valsartan or aliskiren and amlodipine, respectively, report: concurrent use of aliskiren and atorvastatin or ketoconazole or verapamil may lead to an increase in exposure of aliskiren; concurrent use of aliskiren and furosemide may lead to a decrease in furosemide exposure; concurrent use of valsartan and rifampin, cyclosporine, or ritonavir may lead to an increased exposure of valsartan.

Dual blockade of the renin-angiotensin-aldosterone system is associated with increased risk of hypotension, syncope, hyperkalemia, and changes in renal function (including acute renal failure). Closely monitor blood pressure, renal function and electrolytes in patients on ACEs and ARBs.

The ALTITUDE study, a phase III, double-blind trial evaluated the use of aliskiren in addition to conventional therapy in patients with type 2 diabetes and renal impairment, who are at high risk of cardiovascular and renal events.⁵⁸ Patients (n=8,606) were randomized to receive either aliskiren 300 mg or placebo, in addition to conventional therapy, including an ACE inhibitor or ARB. The study was halted early. The Data Monitoring Committee identified a higher incidence of non-fatal stroke, renal complications, hyperkalemia and hypotension after 18 to 24 months of therapy in the aliskiren arm of the study. The study sponsor, Novartis, recommended that ALTITUDE investigators remove aliskiren-based products from their patients' treatment regimen and review their high blood pressure medication. Novartis is also reviewing the findings of other clinical studies involving aliskiren and combination therapies. Novartis recommends healthcare professionals should stop aliskiren-containing medications in diabetic patients who are also taking an ACE inhibitor or an ARB. Alternative antihypertensive therapy should be considered.

ADVERSE EFFECTS

Drug	Naso-pharyngitis	Headache	Dizziness	Peripheral Edema
amlodipine/aliskiren/HCTZ (Amturnide) ⁵⁹	2.6	3.6	3.6	7.1
aliskiren/amlodipine	0.7	3.1	2.4	8.0
aliskiren/HCTZ	2	4	3.4	2
HCTZ/amlodipine	3.4	5.1	1.7	4.1

Drug	Cough	Headache	Dizziness	Edema
amlodipine (n=475)	0.4	2.9	2.3	5.1
benazepril (n=554)	1.8	3.8	1.6	0.9
amlodipine/benazepril (Lotrel) (n=760) ⁶⁰	3.3	2.2	1.3	2.1
placebo (n=408)	0.2	5.6	1.5	2.2

Drug	Naso-pharyngitis	Headache	Fatigue	Peripheral Edema
amlodipine/olmesartan/HCTZ (Tribenzor) ⁶¹ (n=574)	3.5	6.4	4.2	7.7
olmesartan/HCTZ (n=580)	3.4	6.6	5.3	1
amlodipine/olmesartan (n=596)	1.8	7	5.7	7
HCTZ/amlodipine (n=552)	2.9	6	6.5	8.3

Drug	Back pain	Dizziness	Peripheral Edema	Other Edema
amlodipine/telmisartan (Twynsta) (n=789) ⁶²	2.2	3	4.8	< 2
placebo (n=46)	0	2.2	0	nr

Adverse Effects (continued)

Drug	Naso-pharyngitis	URTI	Dizziness	Peripheral Edema
amlodipine/valsartan (Exforge) (n=1,437) ⁶³	4.3	2.9	2.1	5.4
placebo (n=337)	1.8	2.1	0.9	3

URTI – Upper Respiratory Tract Infection

Drug	Dyspepsia	Headache	Dizziness	Edema
amlodipine/valsartan/HCTZ (Exforge HCT) ⁶⁴ (n=582)	2.2	5.2	8.2	6.5
valsartan/HCTZ (n=559)	0.9	5.5	7.2	1.4
amlodipine/valsartan (n=566)	1.1	5.3	2.5	11.5
HCTZ/amlodipine (n=561)	0.4	7.1	4.1	11.2

Drug	Cough	Headache	Dizziness	Edema
verapamil SR/trandolapril (Tarka) ⁶⁵ (n=541)	4.6	8.9	3.1	1.3
placebo (n=206)	2.4	9.7	1.9	2.4

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive.

The overall incidence of adverse reactions for amlodipine/olmesartan (Azor) was similar to that seen with corresponding doses of the individual components and to placebo.⁶⁶ Edema was the most frequently reported adverse effect (\geq three percent) in the amlodipine/olmesartan (Azor) group compared to placebo.

In a placebo-controlled clinical study peripheral edema occurred in 6.2 to 8.9 percent of patients on amlodipine/aliskiren (Tekamlo) versus one percent of those given placebo.⁶⁷ In a long-term safety trial, the safety profile of adverse events was similar to that seen in the short-term controlled trials.

Single episodes of tonic-clonic seizures with loss of consciousness were reported in two patients treated with aliskiren in the clinical trials.⁶⁸

SPECIAL POPULATIONS^{69,70,71,72,73,74, 75,76,77,78}**Pediatrics**

Due to the fixed dose combinations of this class, the Angiotensin Modulators Combinations class does not lend itself to use in pediatric patients. Safety and effectiveness in pediatric patients using the combination products have not been established.

Pregnancy

All products in this review are Pregnancy Category D and all products carry a boxed warning regarding fetal toxicity. When pregnancy is detected, discontinue medication as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.

Renal Impairment

Amlodipine/benazepril (Lotrel), amlodipine/aliskiren/HCTZ (Amturnide), amlodipine/olmesartan/HCTZ (Tribenzor), and amlodipine/valsartan/HCTZ (Exforge HCT) are not recommended in patients with creatinine clearance (CrCl) < 30 mL/min.

There have been no studies of amlodipine/olmesartan (Azor) in patients with renal impairment; there are no specific dosage adjustment recommendations. No dose adjustments for amlodipine/aliskiren (Tekamlo) or amlodipine/aliskiren/HCTZ (Amturnide) are necessary in patients with mild to moderate renal impairment. No data are available regarding amlodipine/aliskiren (Tekamlo) in patients with severe renal impairment. Clinical experience is limited in patients with moderate renal impairment, and there is no clinical experience in patients with severe renal impairment, as patients with a creatinine of 1.7 mg/dL for women and 2 mg/dL for men and/or estimated creatinine clearance < 30 mL/min were excluded from clinical trials. No initial dose adjustment for amlodipine/telmisartan (Twynsta) is required in patients with mild to moderate renal impairment; however, doses should be titrated slowly in patients with severe renal impairment.

Use caution with amlodipine/valsartan (Exforge) when CrCl < 10 mL/min, although it has not been studied in severe renal impairment.

Verapamil SR/trandolapril (Tarka) should be dose adjusted if CrCl < 30 mL/min.

Hepatic Impairment

Patients with hepatic impairment have decreased clearance of amlodipine and verapamil. Caution should be exercised when utilizing amlodipine-containing (Lotrel, Azor, Amturnide, Tekamlo, Tribenzor, Twynsta, Exforge, Exforge HCT) or verapamil-containing (Tarka) products in patients with hepatic impairment. Amlodipine should be started at a dose of 2.5 mg and titrated slowly in this patient population. This strength is not an option with the combination products: Amturnide, Azor, Exforge, Exforge HCT, Tekamlo, Tribenzor, or Twynsta. A dosage adjustment may be required for verapamil SR/trandolapril (Tarka) in patients with hepatic impairment.

Other populations

Black patients receiving ACE inhibitor monotherapy have reported a higher incidence of angioedema compared to non-Blacks. In controlled clinical trials, ACE inhibitors have less effect on blood pressure in Black patients than in non-Blacks.⁷⁹ Amlodipine/olmesartan (Azor) and amlodipine/olmesartan/HCTZ (Tribenzor) have shown to be effective in treating Black patients, with the magnitude of blood pressure reduction in Blacks approaching that observed in the non-black population.

A study evaluated the antihypertensive efficacy and safety of the amlodipine plus aliskiren versus amlodipine alone in self-identified African Americans with stage 2 hypertension in a subgroup of patients with obesity (body mass index ≥ 30 kg/m²; n=292) or metabolic syndrome (n=197) participating in the Aliskiren Amlodipine Combination in African AmERICans with Stage 2 HypertenSion (AACCESS) trial.⁸⁰ Subjects, newly diagnosed and treatment naive or taking three or fewer antihypertensive drugs with a mean sitting systolic blood pressure (msSBP) of 160-199 mm Hg were randomized to receive aliskiren/amlodipine 150/5 mg or amlodipine 5 mg for one week; force-titrated to aliskiren/amlodipine 300/10 mg or amlodipine 10 mg, for an additional seven weeks. Least-square mean reductions from baseline to eight weeks in msSBP, the primary efficacy variable, were significantly higher with aliskiren/amlodipine than with amlodipine in both obese (-33.7 mm Hg versus -27.9 mm Hg; p < 0.001)

and metabolic syndrome subjects (-36.4 mm Hg versus -28.5 mm Hg; $p < 0.001$). Both treatments were well tolerated.

When starting or adding amlodipine for patients ≥ 75 years old or patients with hepatic impairment, the recommended dose of amlodipine is 2.5 mg due to impaired clearance.

Aliskiren-containing medications should be avoided in diabetic patients who are also taking an ACE inhibitor or an ARB.

DOSAGES

Drug	Dosage	Combinations available (Calcium Channel Blocker/Angiotensin Modulator)
amlodipine/aliskiren (Tekamlo) ⁸¹	1 daily	5/150, 5/300, 10/150, 10/300 mg tablets
amlodipine/aliskiren/HCTZ (Amturnide) ⁸²	1 daily	5/150/12.5, 5/300/12.5, 5/300/25, 10/300/12.5, 10/300/25 mg tablets
amlodipine/benazepril (Lotrel) ⁸³	1 daily	2.5/10, 5/10, 5/20, 10/20, 5/40, 10/40 mg capsules
amlodipine/olmesartan (Azor) ⁸⁴	1 daily	5/20, 5/40, 10/20, 10/40 mg tablets
amlodipine/olmesartan/HCTZ (Tribenzor) ⁸⁵	1 daily	5/20/12.5, 5/40/12.5, 5/40/25, 10/40/12.5, 10/40/25 mg tablets
amlodipine/telmisartan (Twynsta) ⁸⁶	1 daily	5/40 mg, 10/40 mg, 5/80 mg, 10/80 mg tablets
amlodipine/valsartan (Exforge) ⁸⁷	1 daily	5/160, 10/160, 5/320, 10/320 mg tablets
amlodipine/valsartan/HCTZ (Exforge HCT) ⁸⁸	1 daily	5/160/12.5, 10/160/12.5, 5/160/25, 10/160/25, 10/320/25 mg tablets
verapamil SR/trandolapril (Tarka) ⁸⁹	1 daily	240/1, 180/2, 240/2, 240/4 mg tablets

CLINICAL TRIALS

Search Strategy

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in the commercially available combinations for this category. Randomized, controlled trials comparing agents within this class for the treatment of hypertension are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

amlodipine/aliskiren (Tekamlo) versus amlodipine versus aliskiren versus placebo

An eight-week, randomized, double-blind, placebo-controlled, multifactorial study of 5,549 patients with mild to moderate hypertension compared the combinations 150 mg/5 mg, 150 mg/10 mg, 300 mg/5 mg and 300 mg/10 mg of aliskiren and amlodipine with their components and placebo.⁹⁰ The combination of aliskiren and amlodipine resulted in placebo-adjusted decreases in systolic/diastolic blood pressure at trough of 14-17/9-11 mm Hg compared to 4-9/3-5 mm Hg for aliskiren alone and 9-14/6-8 mm Hg for amlodipine alone. Treatment with combination therapy resulted overall in significantly greater reductions in diastolic and systolic blood pressure compared to the respective monotherapy components.

Two additional double-blind, active-controlled studies of similar design were conducted in which amlodipine/aliskiren was administered as initial therapy in patients with moderate to severe hypertension (SBP 160-200 mm Hg).⁹¹ Patients were randomized to receive either combination amlodipine/aliskiren or amlodipine monotherapy. The initial dose of amlodipine/aliskiren was 5 mg/150 mg for one week with forced titration to 10 mg/300 mg for seven weeks. The initial dose of amlodipine was 5 mg for one week with forced titration to 10 mg for seven weeks. In one study of 443 Black patients, at the primary endpoint of eight weeks, the treatment difference between amlodipine/aliskiren and amlodipine was 5.2/3.8 mm Hg. In the other study of 484 patients, at the primary endpoint of eight weeks, the treatment difference between amlodipine/aliskiren and amlodipine was 7.1/3.8 mm Hg.

amlodipine/aliskiren/HCTZ (Amturnide) versus aliskiren/amlodipine (Tekamlo) versus aliskiren/HCTZ (Tekturna HCT) versus amlodipine/HCTZ

In a double-blind, active-controlled study in 1,181 treated hypertensive patients, of whom 408 were classified as severely hypertensive (SBP 180-200 mm Hg) were assigned to dual or triple combination therapy.⁹² At study initiation, patients assigned to the dual combination treatments received lower doses of their treatment combination (aliskiren/amlodipine 150/5 mg, aliskiren/HCTZ 150/12.5 mg, or amlodipine/HCTZ 5/12.5 mg). Patients assigned to triple therapy initially received dual therapy of aliskiren/HCTZ 150/12.5 mg, and after three days were titrated to aliskiren/amlodipine/HCTZ 150/5/12.5 mg. All patients in the dual therapy arm continued receiving their initial doses. After four weeks, all patients were titrated to their full target doses of aliskiren/amlodipine/HCTZ 300/10/25 mg, aliskiren/amlodipine 300/10, aliskiren/HCTZ 300/25 mg, or amlodipine/HCTZ 10/25 mg. In the overall patient population, triple therapy reduced SBP/DBP by an additional 9.9/6.3 mm Hg compared to aliskiren/HCTZ; 7.2/3.6 mm Hg compared to amlodipine/HCTZ; and 6.6/2.6 mm Hg compared to aliskiren/amlodipine, all $p < 0.001$. In patients with severely elevated blood pressure, these reductions were greater by 16.3/8.2 mm Hg, 9.6/4.8 mm Hg, and 11.4/4.9 mm Hg, respectively. The antihypertensive effect of triple therapy was similar in patients with and without diabetes, obese and non-obese patients, in patients ≥ 65 years of age and < 65 years of age, and in women and men.

amlodipine/benazepril (Lotrel) and amlodipine (Norvasc) and/or benazepril (Lotensin)

In a multicenter, randomized, double-blind study, 448 patients were randomized to receive one of the following treatments for eight weeks: 1) benazepril 10 mg plus placebo, 2) benazepril 10 mg plus amlodipine 2.5 mg, or 3) benazepril 10 mg plus amlodipine 5 mg.⁹³ Initially, patients underwent a two-week placebo run-in phase followed by a four-week benazepril 10 mg daily run-in phase and then underwent randomization if the mean diastolic BP (DBP) was ≥ 95 mm Hg and < 120 mm Hg after four

weeks of benazepril 10 mg daily. The 24-hour post-dose sitting and standing systolic BP (SBP) and DBP values were statistically lower with combination therapy than with benazepril 10 mg. The tolerability was good in the three treatment groups.

In a multicenter, double-blind, parallel-group study, 308 patients were randomized to one of the following treatments for eight weeks: amlodipine 5 mg/benazepril 20 mg, amlodipine 5 mg, benazepril 20 mg, or placebo once daily for the treatment of hypertension.⁹⁴ The combination had a significantly greater reduction in blood pressure compared to the other monotherapies ($p < 0.001$). A responder rate, as defined as DBP < 90 mm Hg or > 10 mm Hg decrease in mean sitting DBP, of 87 percent was observed for amlodipine/benazepril versus 67.5 percent for amlodipine, 53.3 percent for benazepril, and 15.8 percent for placebo ($p < 0.005$). Edema occurred less often in the amlodipine/benazepril group than in the amlodipine group which has also been observed in other studies.⁹⁵

A double-blind study compared the efficacy and safety of amlodipine 5 to 10 mg and benazepril 40 mg to benazepril 40 mg monotherapy in hypertensive patients ($n = 298$) not controlled on benazepril 40 mg monotherapy.⁹⁶ Patients underwent a two-week washout period and then started on benazepril 40 mg daily. Patients with a mean sitting DBP ≥ 95 mm Hg were randomized to amlodipine 5 mg (then amlodipine 10 mg after four weeks) in addition to benazepril 40 mg or to continue on benazepril 40 mg daily for eight weeks. The mean reduction in sitting BP after eight weeks compared to baseline was $-5/-7$ mm Hg with benazepril and $-17/-14$ mm Hg with amlodipine/benazepril ($p < 0.0001$). Goal attainment of target BP (DBP < 90 mm Hg) was achieved in 80 and 45 percent of amlodipine/benazepril and benazepril groups, respectively ($p < 0.0001$). Both therapies were well tolerated.

A total of 364 patients with stage 2 hypertension were enrolled in a multicenter, double-blind, 12-week trial comparing the efficacy of amlodipine/benazepril combination and amlodipine monotherapy.⁹⁷ Patients were randomized to amlodipine/benazepril 5/20 mg daily and titrated to 10/20 mg daily or amlodipine 5 mg daily titrated to 10 mg daily. The combination therapy achieved a reduction in SBP of greater than -25 to -32 mm Hg in 74.2 percent of patients whereas in the amlodipine group only 53.9 percent of patients achieved the desired BP reductions ($p < 0.0001$). Significantly more patients in the combination therapy group attained BP $< 140/90$ mm Hg (61 percent) compared to 43.3 percent in the monotherapy group ($p = 0.0007$). A significant difference was also seen for those patients achieving a BP $< 135/80$ mm Hg (35.7 versus 19.1 percent of patients, $p = 0.0004$). For patients with baseline SBP > 180 mm Hg, combination therapy had significantly greater reductions in SBP compared to monotherapy (-42.3 versus -30.4 mm Hg, $p = 0.001$). Another study, SELECT, has been published with similar results.⁹⁸

In a randomized, double-blind, multicenter, 12-week study, 70 hypertensive patients with at least one other endothelial dysfunction risk factor were assigned to amlodipine/benazepril 5/20 mg per day (force titrated to 5/40 mg per day) or amlodipine 5 mg per day (force titrated to 10 mg per day).⁹⁹ The study examined combination therapy versus monotherapy in modulating endothelial dysfunction. Both treatment arms resulted in significant median increases from baseline in percentage flow-mediated vasodilation (2 percent versus 1.2 percent, respectively), but between group differences were not statistically significant. Reductions in SBP ($p = 0.0452$) and DBP ($p = 0.0297$) were significantly greater with the combination therapy ($-18.6/-12.3$ mm Hg) versus monotherapy ($-14.8/-9.1$ mm Hg). A correlation between reduction in SBP and change in percentage of flow mediated vasodilation was seen only for combination therapy.

Amlodipine and benazepril were compared to each other and to the combination in a randomized, double-blind, placebo-controlled, multicenter trial.¹⁰⁰ A total of 454 adult patients with hypertension

were randomized to amlodipine 5 mg, benazepril 10 mg, the combination, or placebo once daily for eight weeks. The combination group had greater reductions in sitting DBP from baseline compared to amlodipine ($p<0.03$), benazepril, and placebo (both $p<0.001$). Heart rate did not differ among the groups. Edema was less in the combination group compared to amlodipine (1.7 versus 4.5 percent).

In a multicenter, double-blind, eight-week study, 111 Chinese patients with mild to moderate hypertension were randomized to amlodipine/benazepril 2.5/5 mg daily or amlodipine 5 mg daily.¹⁰¹ Blood pressure was obtained after four weeks of therapy and then the dose was titrated up if BP was $> 140/90$ mm Hg. After eight weeks of therapy, BP control rates were similar with 56 percent in the combination group and 46.2 percent in the amlodipine monotherapy group ($p=0.32$). Fixed-dose combination resulted in similar reductions in sitting SBP and DBP compared with monotherapy (SBP: -19.3 mm Hg versus -20.9 mm Hg; DBP: -9.2 mm Hg versus -11.3 mm Hg; both $p=NS$). Safety profiles did not differ between groups, but cough was more common in the combination group (11 percent versus zero percent; $p=0.013$).

amlodipine/benazepril (Lotrel) versus benazepril/hydrochlorothiazide (HCTZ) (Benicar HCT)

The ACCOMPLISH trial investigated if the combination of benazepril plus amlodipine would be more effective in reducing the rate of cardiovascular events than treatment with benazepril plus HCTZ in 11,506 patients with hypertension who were at high risk for cardiovascular events.¹⁰² In a randomized, double-blind trial, the baseline characteristics of the two groups were similar with mean body mass index (BMI) of 31 kg/m² and 60 percent of patients had a diagnosis of diabetes.¹⁰³ The primary endpoint was the composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, and coronary revascularization. Mean BP after dose adjustments were 131.6/73.3 mm Hg in the amlodipine/benazepril group and 132.5/74.4 mm Hg in the benazepril/HCTZ group. After 36 months, the trial was terminated. Primary outcome events occurred in 552 patients (9.6 percent) in the amlodipine/benazepril group and 679 patients (11.8 percent) in the benazepril/HCTZ group (11.8 percent) with an absolute risk reduction with amlodipine/benazepril therapy of 2.2 percent and a relative risk reduction of 19.6 percent (hazard ratio, 0.80, 95% confidence interval [CI], 0.72 to 0.90; $p<0.001$). For the secondary endpoint of death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke, the hazard ratio was 0.79 (95% CI, 0.67 to 0.92; $p=0.002$). An additional analysis found that patients in the United States, Caucasians, and patients taking lipid-lowering therapy were most likely to reach BP targets with combination therapy.¹⁰⁴ The combination of amlodipine/benazepril was superior to the benazepril-HCTZ combination in reducing cardiovascular events in patients with hypertension who were at high risk for such events.

amlodipine/valsartan (Exforge) versus amlodipine (Norvasc) or valsartan (Diovan)

Efficacy of the combination of amlodipine and valsartan were compared to the individual components in two multicenter, eight-week, randomized, double-blind, parallel-group trials.¹⁰⁵ In the first study, 1,911 patients were randomized to receive amlodipine 2.5 or 5 mg once daily, valsartan 40 to 320 mg once daily, or the combination of amlodipine 2.5 or 5 mg plus valsartan 40 to 320 mg once daily or placebo for eight weeks. In the second study, 1,250 patients were randomized to amlodipine 10 mg once daily, valsartan 160 or 320 mg once daily, or the combination of amlodipine 10 mg with valsartan 160 or 320 mg once daily or placebo for eight weeks. The primary efficacy parameter was the change

from baseline in mean sitting DBP at the end of the study. A positive dose response was observed for all combinations. With the exception of a few combinations that included amlodipine 2.5 mg, the combination regimens in both studies were associated with significantly greater reductions in mean sitting DBP and mean sitting SBP compared with their individual components and placebo ($p < 0.05$). The highest response rate, defined as patients achieving mean sitting DBP < 90 mm Hg or > 10 mm Hg decrease from baseline, in the first study was associated with the highest dose of combination therapy (amlodipine 5 mg/valsartan 320 mg: 91.3 percent). Amlodipine 5 mg, valsartan 320 mg, and placebo were associated with response rates of 71.9 percent, 73.4 percent, and 40.9 percent, respectively. In the second study, the response rates were similar for the two doses of combination therapy (amlodipine 10 mg/valsartan 160 mg: 88.5 percent; amlodipine 10 mg/valsartan 320 mg: 87.5 percent). Amlodipine 10 mg was associated with a response rate of 86.9 percent; valsartan 160 and 320 mg were associated with response rates of 74.9 percent and 72 percent, respectively; and placebo was associated with a response rate of 49.3 percent. Peripheral edema was reported less frequently with the combination therapy than with amlodipine monotherapy (5.4 versus 8.7 percent, respectively; $p = 0.014$). Combination therapy had a significantly higher incidence of peripheral edema compared to valsartan monotherapy (5.4 percent versus 2.1 percent, respectively; $p < 0.001$) but not significantly different than placebo (three percent).

amlodipine/valsartan (Exforge)

In a randomized, double-blind, multicenter study, 894 patients whose blood pressure was uncontrolled by monotherapy were switched to amlodipine/valsartan 5/160 mg or 10/160 mg.¹⁰⁶ After 16 weeks, BP control (BP $< 140/90$ mm Hg or $< 130/80$ mm Hg for diabetics) was achieved in 72.7 percent (95% CI, 68.6 to 76.9) of patients receiving amlodipine/valsartan 5/160 mg and in 74.8 percent (95% CI, 70.8 to 78.9) receiving amlodipine/valsartan 10/160 mg. Incremental reductions from baseline in mean sitting systolic and diastolic BP were significantly greater with the higher dose (20 ± 0.7 versus 17.5 ± 0.7 mm Hg, $p = 0.0003$ and 11.6 ± 0.4 versus 10.4 ± 0.4 mm Hg, $p = 0.0046$). Peripheral edema was the most frequent adverse event.

A multicenter, randomized, double-blind, active-controlled study in patients with essential hypertension was conducted to demonstrate additional BP-lowering effects of amlodipine/valsartan combination in patients whose BP was not adequately controlled on valsartan alone.¹⁰⁷ After a washout period followed by a single-blind valsartan 160 mg run-in period, patients with mean sitting DBP ≥ 90 mm Hg and < 110 mm Hg were randomized to receive amlodipine/valsartan (10/160 mg or 5/160 mg) or valsartan 160 mg for eight weeks. The primary efficacy variable was change from baseline in mean DBP at study end. Secondary efficacy variables included change from baseline in mean sitting SBP, responder rate (mean DBP < 90 mm Hg or ≥ 10 mm Hg reduction from baseline), and DBP control rate (mean DBP < 90 mm Hg). Of 1,136 patients enrolled in the single-blind phase, 947 (mean age: 54.6 years) were randomized. Greater reductions in mean SBP/DBP were observed in both amlodipine/valsartan combinations (10/160 mg: 14.3/11.5 mm Hg, 5/160 mg: 12.2/9.6 mm Hg; both $p < 0.0001$) compared to valsartan 160 mg (8.3/6.7 mm Hg). Responder rates were higher in both combination therapy groups (10/160 mg: 81 percent [$p < 0.0001$]; 5/160 mg: 68 percent [$p = 0.0018$], respectively) compared to monotherapy (57 percent). Peripheral edema was the most frequent adverse event reported in amlodipine/valsartan 10/160 mg (9.1 percent), 5/160 mg (0.9 percent), and valsartan 160 mg (1.3 percent).

amlodipine/valsartan (Exforge) versus amlodipine as initial therapy

Two double-blind, active-controlled studies were conducted in which the combination of amlodipine/valsartan was administered as initial therapy.¹⁰⁸ In one study, a total of 572 Black patients with moderate to severe hypertension were randomized to receive either combination amlodipine/valsartan or amlodipine monotherapy for 12 weeks. The initial dose of amlodipine/valsartan was 5/160 mg for two weeks with forced titration to 10/160 mg for two weeks, followed by optional titration to 10/320 mg for four weeks and optional addition of HCTZ 12.5 mg for four weeks. The initial dose of amlodipine was 5 mg for two weeks with forced titration to 10 mg for two weeks, followed by optional titration to 10 mg for four weeks and optional addition of HCTZ 12.5 mg for four weeks. At the primary endpoint of eight weeks, the treatment difference between amlodipine/valsartan and amlodipine was 6.7/2.8 mm Hg in favor of the combination product.

In the other study of similar design, a total of 646 patients with moderate to severe hypertension (SBP of ≥ 160 mm Hg and < 200 mm Hg) were randomized to receive either combination amlodipine/valsartan or amlodipine monotherapy for eight weeks.¹⁰⁹ The initial dose of amlodipine/valsartan was 5/160 mg for two weeks with forced titration to 10/160 mg for two weeks, followed by the optional addition of HCTZ 12.5 mg for four weeks. The initial dose of amlodipine was 5 mg for two weeks with forced titration to 10 mg for two weeks followed by the optional addition of HCTZ 12.5 mg for four weeks. At the primary endpoint of four weeks, the treatment difference between amlodipine/valsartan and amlodipine was 6.6/3.9 mm Hg in favor of the combination product.

This multicenter, randomized, double-blind, active-controlled study evaluated the efficacy and tolerability of amlodipine/valsartan combination therapy in patients with essential hypertension (n=944) who were not adequately controlled on amlodipine monotherapy.¹¹⁰ Patients with mean sitting diastolic blood pressure (msDBP) ≥ 90 mm Hg and < 110 mm Hg were randomized to receive amlodipine/valsartan 10/160 mg (n=473) or amlodipine 10 mg (n=471) for eight weeks after a washout period followed by a single-blind amlodipine 10 mg run-in period. The primary efficacy variable was change from baseline in msDBP at study endpoint. Secondary endpoints were change from baseline in mean sitting systolic blood pressure (msSBP), responder rate (msDBP < 90 mm Hg or ≥ 10 mm Hg reduction from baseline) and DBP control rate (msDBP < 90 mm Hg). Combination therapy resulted in greater reductions ($p < 0.0001$) from baseline in msSBP/msDBP (12.9/11.4 mm Hg) compared to monotherapy (10/9.3 mm Hg). Responder rate was significantly greater ($p = 0.0011$) with combination therapy (79 percent) compared to monotherapy (70.1 percent), and the percentage of patients with controlled DBP was also higher ($p < 0.0001$) with combination therapy (77.8 percent) compared to monotherapy (66.5 percent). The incidence of peripheral edema was slightly higher with amlodipine monotherapy (9.4 percent) compared to combination therapy (7.6 percent).

amlodipine/valsartan (Exforge) versus lisinopril/HCTZ (Prinzide® or Zestoretic®)

The safety profile of the combination of amlodipine and valsartan was compared with lisinopril plus hydrochlorothiazide in patients with stage 2 hypertension over six weeks.¹¹¹ In the randomized, double-blind trial, 130 patients received amlodipine 5 to 10 mg plus valsartan 160 mg once daily or lisinopril 10 to 20 mg plus HCTZ 12.5 mg once daily for six weeks. All therapies were well tolerated, and most adverse effects were not related to the study drug. Efficacy, a secondary endpoint, was evaluated by the changes from baseline for mean sitting DBP and SBP. After six weeks, both amlodipine/valsartan and lisinopril/HCTZ groups had significant reductions from baseline for mean sitting SBP (-35.8 and

-31.8 mm Hg, respectively, both $p < 0.001$) and for mean sitting DBP (-28.6 and -27.6 mm Hg, respectively, both $p < 0.001$).

verapamil SR/trandolapril (Tarka) and trandolapril (Mavik) and/or verapamil SR

In a randomized, double-blind placebo-controlled trial, trandolapril, verapamil SR, the combination of the two agents, and placebo were evaluated for antihypertensive efficacy in 631 adults with hypertension.¹¹² Both single agent groups lowered BP more than placebo. The combination lowered BP more than either agent alone. All groups had similar adverse events, and therapies were well tolerated. Two other prospective, double-blind trials found similar results.^{113,114}

The antihypertensive efficacy of verapamil SR and trandolapril were evaluated in 438 patients with high normal BP or borderline isolated systolic hypertension and type 2 diabetes.¹¹⁵ The patients were randomized to verapamil SR plus trandolapril, trandolapril, or placebo and followed for 16 weeks in a double-blind fashion. Doses were doubled if BP goals were not achieved after eight weeks ($< 130/85$ mm Hg). Both active treatment groups significantly lowered BP compared to placebo (both $p < 0.001$). However, no significant difference in the control of SBP was seen between the two active treatment groups. The percentage of patients achieving BP $< 130/85$ mm Hg was 36.5 percent in the trandolapril group, 37.8 percent in the combination group, and 14.9 percent in the placebo group ($p = 0.009$, combination and trandolapril groups versus placebo). Control rate for DBP (< 85 mm Hg) was significantly higher in the combination group (88.8 percent) when compared with trandolapril (79.1 percent) or placebo (63.5 percent; $p = 0.002$). Withdrawal rates were similar in all groups.

The BENEDICT study assessed trandolapril and verapamil, alone or in combination, for efficacy in preventing microalbuminuria in 1,204 patients with hypertension, type 2 diabetes, and normal urinary albumin excretion.¹¹⁶ Patients were randomized to three years of trandolapril 2 mg daily plus verapamil SR 180 mg daily, trandolapril 2 mg daily, verapamil SR 240 mg daily, or placebo in a double-blind fashion. The primary outcome was the development of microalbuminuria (> 20 mcg/min at two visits). Microalbuminuria was observed in 5.7 percent of the combination group, six percent in trandolapril monotherapy, 11.9 percent in verapamil monotherapy and 10 percent in the placebo group. Trandolapril plus verapamil and trandolapril monotherapy reduced the risk of the development of microalbuminuria to a similar extent and greater than placebo. Verapamil was similar to placebo.

The INVEST trial compared the combination of verapamil SR and trandolapril with atenolol and hydrochlorothiazide in 22,576 hypertensive coronary artery disease (CAD) patients over 50 years old.¹¹⁷ In the randomized, open-label, blinded endpoint, multinational trial, patients were randomized to verapamil SR or atenolol. After a mean follow-up of 2.7 years, the occurrence of all-cause death, nonfatal myocardial infarction (MI), or nonfatal stroke, and BP control and goal attainment were similar in both groups. While the study did not specifically provide the combination tablet form of verapamil SR and trandolapril, INVEST did provide efficacy information regarding the co-administration of verapamil SR and trandolapril in a large clinical trial.

A subgroup of patients without diabetes from the randomized, double-blinded INVEST trial at study entry were investigated for newly diagnosed diabetes during follow-up.¹¹⁸ Newly diagnosed diabetes was less frequent in the verapamil SR versus atenolol group (7 percent versus 8.2 percent, hazard ratio [HR] 0.85, 95% CI, 0.76 to 0.95, $p < 0.01$). Some of the characteristics of risk for newly diagnosed diabetes included United States residence, left ventricular hypertrophy, previous stroke/transient

ischemic attack, and Hispanic ethnicity. Addition of trandolapril to verapamil SR decreased diabetes risk and addition of hydrochlorothiazide to atenolol increased the diabetes risk.

Another substudy of INVEST evaluated 7,218 patients with prior MI for the primary outcome of time to first occurrence of death (all-cause), nonfatal MI, or nonfatal stroke.¹¹⁹ Secondary outcomes included death, total MI (fatal and nonfatal), and total stroke (fatal and nonfatal) considered separately. During the 2.8 ± 1 years of follow-up, patients assigned to the verapamil-SR-based and atenolol-based groups had comparable blood pressure control, and the incidence of the primary outcome was equivalent. There was no difference between the two groups for the outcomes of either death or total MI. More patients reported excellent/good well-being (82.3 percent versus 78 percent, $p=0.02$) at 24 months with a trend toward less incidence of angina pectoris (12 percent versus 14.3 percent, adjusted $p=0.07$), nonfatal stroke (1.4 percent versus 2 percent; $p=0.06$), and total stroke (2 percent versus 2.5 percent, $p=0.18$) in the verapamil-SR-based group. In this study of hypertensive patients with prior MI, a verapamil SR-based group was equivalent to a beta-blocker-based group for blood pressure control and prevention of cardiovascular events.

amlodipine/olmesartan (Azor) versus olmesartan initial therapy

A randomized, double-blind, parallel-group, multicenter trial included patients with moderate to severe hypertension ($\geq 160/100$ mm Hg) and investigated the additional efficacy on BP reduction and BP goal rates ($<140/90$ mm Hg for patients without diabetes mellitus, $<130/80$ mm Hg for patients with diabetes) when amlodipine 5 or 10 mg per day was added to olmesartan 20 mg/day in patients not adequately controlled on olmesartan alone¹²⁰. After an eight week open-label olmesartan 20 mg monotherapy period, 538 patients with BP $\geq 140/90$ mm Hg were randomized to eight weeks of olmesartan/placebo, olmesartan/amlodipine 20 mg/5 mg or olmesartan/amlodipine 20 mg/10 mg. The adjusted mean change in seated DBP (SeDBP) from baseline was -7.6 mm Hg for olmesartan/placebo, -10.4 mm Hg for olmesartan/amlodipine 20 mg/5 mg ($p=0.0006$ versus olmesartan/placebo) and -10.9 mm Hg for olmesartan/amlodipine 20 mg/10 mg ($p<0.0001$ versus olmesartan/placebo). Mean changes in SeSBP from baseline with olmesartan/placebo, olmesartan/amlodipine 20 mg/5 mg, and olmesartan/amlodipine 20 mg/10 mg were -10.8, -16.1, and -16.7 mm Hg, respectively ($p<0.0001$ for both dose regimens versus olmesartan/placebo). BP goal rates were higher with olmesartan/amlodipine 20 mg/5 mg and olmesartan/amlodipine 20 mg/10 mg (44.5 percent and 45.8 percent, respectively; $p=0.0011$ and $p=0.0004$, respectively) versus olmesartan/placebo (28.5 percent). Combination therapy was well tolerated, and the incidence of drug-related adverse events was 8.9 percent for olmesartan/placebo, 7.7 percent for olmesartan/amlodipine 20 mg/5 mg, and 11.3 percent for olmesartan/amlodipine 20 mg/10 mg ($p=0.49$).

amlodipine/olmesartan (Azor) versus amlodipine (Norvasc) or olmesartan (Benicar)

In a multicenter, randomized, double-blind trial, the efficacy and tolerability of the combination of olmesartan and amlodipine were compared to the individual components in 1,940 patients with hypertension.¹²¹ Patients were either untreated or underwent a two-week wash-out period and had a seated DBP of 95 – 120 mm Hg. The mean baseline BP was 164/102 mm Hg, and 79.3 percent of patients had stage 2 hypertension. Patients were randomized to olmesartan 10, 20 or 40 mg daily, amlodipine 5 or 10 mg daily, each possible combination of amlodipine/olmesartan or placebo. The primary endpoint was the change from baseline in seated DBP after eight weeks of treatment. Combination therapy with amlodipine/olmesartan had dose-dependent reductions in seated DBP

ranging from -13.8 mm Hg to -19 mm Hg. The secondary endpoint, seated SBP, reductions observed in the combination therapy group ranged from -23.6 mm Hg to -30.1 mm Hg). Both SBP and DBP reductions with the combination therapy were significantly greater than those observed with either monotherapy ($p < 0.001$). The percentages of patients achieving BP goal attainment were significantly higher with combination therapy compared to monotherapy ($p < 0.005$). Combination therapy was well tolerated. The most common adverse events were edema and headache. Percentages for edema ranged from 9.9 percent with olmesartan 20 mg to 36.8 percent with amlodipine 10 mg compared to 12.3 percent with placebo. Percentages of patients reporting headache ranged from 2.5 percent in the amlodipine/olmesartan 10-5 mg group to 8.7 percent in the olmesartan 20 mg group; a total of 14.2 percent of patients receiving placebo reported headache.

amlodipine/olmesartan/HCTZ (Tribenzor) versus amlodipine (Norvasc) or olmesartan (Benicar)

The antihypertensive efficacy of triple combination therapy with amlodipine/olmesartan/HCTZ was studied in a double-blind, active-controlled study in hypertensive patients ($n = 2,492$).¹²² Patients were randomized to receive olmesartan/amlodipine/HCTZ 40/10/25 mg, olmesartan/amlodipine 40/10 mg, olmesartan/HCTZ 40/25 mg, or amlodipine/HCTZ 10/25 mg for two to four weeks. Patients were then randomized to continue on the dual therapy they were receiving or to receive triple therapy. After eight weeks of treatment, the triple combination therapy produced greater reductions in both systolic and diastolic blood pressures ($p < 0.0001$) compared to each of the dual combination therapies. Reductions in seated blood pressure measures were: 8.4/4.5 mm Hg for HCTZ 25 mg added to olmesartan 40/amlodipine 10 mg; 7.6/5.4 mm Hg for amlodipine 10 mg added to olmesartan 40 /HCTZ 25 mg; and 8.1/5.4 mm Hg for olmesartan 40 mg added to amlodipine 10 /HCTZ 25 mg. A total of 440 patients participated in the ambulatory blood pressure monitoring portion of the study. Over the 24-hour period, there was a greater reduction in diastolic and systolic ambulatory blood pressure for olmesartan/amlodipine/hydrochlorothiazide 40/10/25 mg compared to each of the dual combination therapies.

amlodipine/telmisartan (Twynta) versus amlodipine (Norvasc) or telmisartan (Micardis)

A randomized 4 x 4 factorial study evaluated the efficacy and safety of telmisartan plus amlodipine in 1,461 patients with stage 1 or 2 hypertension (BP $153.2 \pm 12.1/101.7 \pm 4.3$ mm Hg).¹²³ Patients were randomized to one of 16 treatment groups using combinations of dose ranges of telmisartan 0 to 80 mg and amlodipine of 0 to 10 mg daily for eight weeks. Blood pressure reductions were greater with combination therapy than respective monotherapies, with the greatest mean systolic/diastolic BP reductions seen in the telmisartan 80 mg plus amlodipine 10 mg group (-26.4/-20.1 mm Hg; $p < 0.05$ compared with both monotherapies). BP control was also greatest in the telmisartan 80 mg/amlodipine 10 mg group (76.5 percent [overall control] and 85.3 percent [DBP control]), and BP response rates were more than 90 percent with this combination. Peripheral edema was most common in the amlodipine 10 mg group (17.8 percent); however, this rate was notably lower when amlodipine was used in combination with telmisartan: 11.4 percent (telmisartan 20 mg/amlodipine 10 mg), 6.2 percent (telmisartan 40 mg/amlodipine 10 mg, and 11.3 percent (telmisartan 80 mg/amlodipine 10 mg).

A placebo-controlled, double-blind, 4x4 factorial design trial in 562 patients with clinic diastolic BP at least 95 and 119 mm Hg or less were randomized to receive telmisartan 0, 20, 40, or 80 mg and/or amlodipine 0, 2.5, 5, or 10 mg.¹²⁴ Ambulatory BP monitoring was performed at baseline and after eight weeks of treatment; the end points of interest were the changes from baseline in 24-h systolic and diastolic BP. Secondary end points included the proportion of responders (≥ 10 mm Hg BP reduction from baseline and/or $< 130/80$ mm Hg mean 24-h BP) and controlled patients ($< 130/80$ mm Hg mean 24-h BP). Combination therapies of telmisartan and amlodipine lowered 24-h BP to a larger extent than the corresponding monotherapies at all doses. Mean reductions from baseline in 24-h BP for the combination of the highest doses of telmisartan 80 mg and amlodipine 10 mg were $-22.4/-14.6$ mm Hg versus $-11.9/-6.9$ mm Hg for amlodipine 10 mg and $-11/-6.9$ mm Hg for telmisartan 80 mg ($p < 0.0001$ for each comparison). In addition, BP response and control rates (24-h BP $< 130/80$ mm Hg) were significantly higher with the combination therapy versus the monotherapy groups.

Patients ($n=1,078$) with a DBP ≥ 100 mm Hg at baseline were included in a subgroup analysis of the above study.¹²⁵ The primary endpoint was the change in the in-clinic seated trough cuff DBP from baseline to study end for combination versus respective monotherapies. Secondary endpoints included the change in the in-clinic seated trough systolic BP (SBP), BP response, and control rates. In-clinic DBP and SBP reductions were greater with combination therapies than respective monotherapies, with the greatest least-square mean SBP/DBP reductions ($-26.5 \pm 1.2/-21 \pm 0.8$ mm Hg) observed in the telmisartan 80 mg plus amlodipine 10 mg group; 77 percent and 85 percent of patients in this treatment group achieved BP control ($< 140/90$ mm Hg) and DBP control (< 90 mm Hg), respectively. Peripheral edema was reported in 17.2 percent of patients in the amlodipine 10 mg group; however, this was substantially lower when telmisartan was used in combination: seven percent (telmisartan 40 mg/amlodipine 10 mg) and 9.5 percent (telmisartan 80 mg/ amlodipine 10 mg).

A comparative, Phase III, 12-week, multicenter, prospective, randomized, double-blind study in 210 Indian patients with established stage 2 hypertension was conducted to evaluate the efficacy and tolerability of the combination of telmisartan 40 mg and amlodipine 5 mg versus amlodipine 5 mg monotherapy over 12 weeks.¹²⁶ Primary efficacy end points were reduction in clinical SBP/DBP from baseline to study end and number of responders, defined as those who achieved target SBP/ DBP ($< 130/80$ mm Hg) at study end. A total of 203 patients completed the study. At 12 weeks, statistically significant percentage reductions from baseline within groups and between groups were observed in SBP (combination treatment [-27.4 percent]; amlodipine [-16.6 percent]) and DBP (combination treatment [-20.1 percent]; amlodipine [-13.3 percent]) (all, $p < 0.05$). Response rates were 87.3 percent in the combination treatment group and 69.3 percent in the amlodipine group ($p < 0.05$). The prevalence of adverse events was not significantly different between the two treatment groups.

META-ANALYSIS

A meta-analysis of 17 randomized controlled trials including 3,291 patients found that the combination treatment of amlodipine and ACE inhibitors resulted in a greater reduction of both systolic blood pressure (SBP) [weighted mean difference (WMD) 5.72, 95% CI, 4.10 to 7.33] and diastolic blood pressure (DBP) (WMD 3.62, 95% CI, 4.85 to 2.39) than monotherapy.¹²⁷ The combination treatment also generated significantly greater reductions for the mean ambulatory SBP and DBP during the full 24 hours (WMD: SBP 4.24, 95% CI, 6.82 to 1.67; DBP 2.23, 95% CI, 3.73 to 0.69), but not for the trough (WMD: SBP 4.52, 9.56 to -0.51 ; DBP 3.7, 7.65 to -0.25). The hypertension therapeutic control (SPB < 140 mm Hg, DBP < 90 mm Hg) rate for the combination treatment is higher than that for monotherapy

[relative risk (RR): 1.36, 95% CI, 1.07 to 1.73]. The combination treatment also resulted in a lower overall rate of adverse events (RR: 0.86, 95% CI, 0.75 to 0.99) and edema (RR: 0.40, 95% CI, 0.29 to 0.56), but a higher rate of cough (RR: 3.28, 95% CI, 2.03 to 5.29) as compared with monotherapy.

SUMMARY

Most patients require more than one medication to achieve adequate BP control. The combinations of an angiotensin modulator and calcium channel blocker or the combination of an angiotensin receptor blocker and a renin inhibitor have been shown to be more effective than either agent alone for the treatment of hypertension. The combination products appear similar in efficacy and safety; however, comparative trials are lacking.

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