

# Angiotensin Modulators Combinations Review

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## Angiotensin Modulators Combinations Review

### **FDA-Approved Indications**

<b>Drug</b>	<b>Manufacturer</b>	<b>Indication(s)</b>
amlodipine / benazepril (Lotrel <sup>®</sup> ) <sup>1</sup>	generic, Novartis	Hypertension (not as initial therapy)
amlodipine / olmesartan (Azor <sup>™</sup> ) <sup>2</sup>	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 / telmisartan (Twynta <sup>®</sup> ) <sup>3</sup>	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 <sup>®</sup> ) <sup>4</sup>	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 <sup>®</sup> ) <sup>5</sup>	Novartis	Hypertension (not initial therapy)
valsartan / aliskiren (Valturna <sup>®</sup> ) <sup>6</sup>	Novartis	Initial treatment of hypertension in patients who will likely require multiple medications for blood pressure control or as add-on therapy in patients whose blood pressure is not adequately controlled
verapamil SR / trandolapril (Tarka <sup>®</sup> ) <sup>7</sup>	Abbott	Hypertension (not as initial therapy)

### **Overview**

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) treatment algorithm for hypertension includes combination therapy as a therapeutic option.<sup>8</sup> Most hypertensive patients require at least two

medications to achieve adequate blood pressure (BP) reduction as seen in a large clinical trial.<sup>9</sup>

### **Pharmacology**

These agents are a combination of 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, or a direct renin inhibitor (DRI). ACE inhibitors included in this class of combination products include benazepril (Lotensin<sup>®</sup>) and trandolapril (Mavik<sup>®</sup>).

Aliskiren (Tekturna<sup>®</sup>) is a direct 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).<sup>10</sup>

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.<sup>11</sup> There is also a possible local action within the vascular wall that is responsible for blood pressure reduction.<sup>12</sup>

Olmesartan (Benicar<sup>®</sup>), telmisartan (Micardis<sup>®</sup>), and valsartan (Diovan<sup>®</sup>) 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.<sup>13,14</sup> ARBs block the vasoconstrictive and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT<sub>1</sub> 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<sup>®</sup>) is a potent vasodilator and can increase or have a neutral effect on vascular permeability.<sup>15</sup> 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.<sup>16,17</sup>

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 C<sub>max</sub> are seen with verapamil.<sup>18</sup>

Brand Name	Generic Name	Bioavailability (%)	Half-Life (hr)	Metabolites	Excretion (%)
Lotrel <sup>19</sup>	amlodipine	64-90	~ 48	extensively metabolized	Urine: 70
	benazepril	> 37	10-11	benazeprilat (approx. 100%)	Primarily urine
Twynsta <sup>20</sup>	amlodipine	64-90	30-50	extensively converted to inactive metabolites	Urine: 70
	telmisartan	42-58	24	Metabolized to glucuronide conjugate	Feces: > 97
Azor <sup>21</sup>	amlodipine	64-90	45	extensively metabolized	Urine: 70
	olmesartan	26	7	none significant	Urine: 35-50
Exforge <sup>22</sup>	amlodipine	64-90	30-50	extensively metabolized	Urine: 70
	valsartan	25	6	20% of dose converted to metabolites	Urine: 13 Feces: 83
Exforge HCT <sup>23,24</sup>	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
Valturna <sup>25,26,27</sup>	aliskiren	~2.5	34	Metabolized	Urine: ~25
	valsartan	25	12	20% of dose converted to metabolites	Urine: 13 Feces: 83
Tarka <sup>28</sup>	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**<sup>29,30,31,32,33,34,35</sup>

All of these products are contraindicated in pregnancy during the second and third trimesters due to the ACE inhibitor or ARB component. ACE inhibitors have been associated with injury and even death to the developing fetus.<sup>36</sup> Angiotensin Modulators combination products should be discontinued as soon as possible in pregnant women. Amlodipine/benazepril (Lotrel) lists Pregnancy Category D for all trimesters.

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. Hypersensitivity to any of these products is considered a contraindication.

Increases in serum creatinine or blood urea nitrogen have been reported in ACE inhibitors in hypertensive patients with unilateral or bilateral renal artery stenosis. A similar effect should be anticipated with ARBs. No such issues have been seen with the use of aliskiren/valsartan; however, long term studies involving patients with renal artery stenosis are lacking. Effects similar to ACE inhibitors should be expected.

Due to the verapamil component, verapamil SR/trandolapril (Tarka) is contraindicated in patients with severe left ventricular dysfunction (LVD), hypotension (SBP < 90 mmHg) 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/valsartan/HCTZ (Exforge HCT) is 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.

Rarely initiation or increased doses of amlodipine may increase the frequency, intensity or duration of angina or cause acute myocardial infarction, particularly in patients with severe obstructive coronary artery disease.

Aliskiren has been associated with angioedema of the face, extremities, lips, tongue, glottis and/or larynx and may require hospitalization. This has occurred in patients without prior history of angioedema with Angiotensin Converting Enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB), and may occur at anytime during therapy.

### **Drug Interactions**<sup>37,38,39,40,41,42,43</sup>

ACE inhibitors interact with azathioprine, cyclosporine, lithium, NSAIDs, potassium sparing diuretics, trimethoprim, and eplerenone (Inspra<sup>®</sup>). Concurrent use of loop and thiazide diuretics can increase the risk of hypovolemia and increase the risk of nephrotoxicity. Verapamil can interact with digoxin, lithium, erythromycin, clarithromycin, beta-blockers, carbamazepine, rifampin, phenobarbital, cyclosporine, theophylline, and select antiarrhythmic agents. Olmesartan (Benicar) and valsartan (Diovan) have not been shown to cause clinically significant pharmacokinetic drug interactions with other 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 is not recommended as the blood concentrations of aliskiren may be significantly increased.

No drug interaction studies have been conducted with Valturna and other drugs, although studies with the individual components, aliskiren and valsartan report: concurrent use of aliskiren and atorvastatin or ketoconazole 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.

**Adverse Effects**

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) <sup>44</sup>	3.3	2.2	1.3	2.1
placebo (n=408)	0.2	5.6	1.5	2.2

Drug	Orthostatic Hypotension	Back pain	Dizziness	Edema
amlodipine/telmisartan (Twynsta) (n=789) <sup>45</sup>	6.3	2.2	3	4.8
placebo (n=46)	4.3	0	2.2	0

Drug	Naso-pharyngitis	URTI	Dizziness	Edema
amlodipine/valsartan (Exforge) (n=1,437) <sup>46</sup>	4.3	2.9	2.1	5.4
placebo (n=337)	1.8	2.1	0.9	3

URTI – Upper Respiratory Tract Infection

**Adverse Effects (continued)**

Drug	Dyspepsia	Headache	Dizziness	Edema
amlodipine/valsartan/HCTZ (Exforge HCT) <sup>47</sup> (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	Fatigue	URTI	Vertigo	UTI
valsartan/aliskiren (Valturna) <sup>48</sup>	2.6	1.4	1.1	1.4
placebo	1.4	1.1	0.3	0.6

UTI = urinary tract infection

Drug	Cough	Headache	Dizziness	Edema
verapamil SR/trandolapril (Tarka) <sup>49</sup> (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.

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.<sup>50</sup> Edema was the most frequently reported adverse effect ( $\geq$  three percent) in the amlodipine/olmesartan (Azor) group compared to placebo.

**Special Populations**<sup>51,52,53,54,55,56,57</sup>

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

Angiotensin Modulators combinations are contraindicated in second and third trimesters of pregnancy due to the ACE inhibitor or ARB component. Amlodipine/benazepril (Lotrel),

amlodipine/valsartan (Exforge), valsartan/aliskiren (Valturna), and amlodipine/valsartan/HCTZ (Exforge HCT) are Pregnancy Category D in all trimesters. Amlodipine/olmesartan (Azor), amlodipine/telmisartan (Twynsta), and verapamil SR/trandolapril (Tarka) are Pregnancy Category C in the first trimester and Pregnancy Category D in the second and third trimesters.

#### Renal Impairment

Amlodipine/benazepril (Lotrel) 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 valsartan/aliskiren (Valturna) are necessary in patients with mild to moderate 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

Amlodipine/benazepril (Lotrel) and verapamil SR/trandolapril (Tarka) should be dose adjusted in patients with hepatic impairment.

Caution should be exercised for amlodipine/olmesartan (Azor) in severe hepatic impairment. Patients with hepatic impairment have decreased clearance of amlodipine; therefore, amlodipine should be started at a dose of 2.5 mg in this patient population. The lowest dose of amlodipine/olmesartan (Azor) is 5/20 mg; therefore, this product is not recommended as initial therapy in patients with hepatic impairment. The lowest dose of amlodipine/telmisartan (Twynsta) is 40/5 mg and therefore, initial therapy with Twynsta is not recommended.

Caution should be exercised when utilizing amlodipine/valsartan (Exforge) in patients with severe hepatic impairment and lower initial doses may be required.

Amlodipine/valsartan/HCTZ (Exforge HCT) should be avoided in patients with severe hepatic impairment; however, patients with lesser degrees of hepatic impairment may use this agent cautiously and should be monitored for worsening hepatic or renal function and adverse effects.

No dose adjustments for valsartan/aliskiren (Valturna) are necessary in patients with mild to moderate hepatic impairment. Clinical experience is limited in patients with severe 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.<sup>58</sup> Amlodipine/valsartan (Azor) was effective in treating black patients, with the magnitude of blood pressure reduction in blacks approaching that observed in the non-black population.



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

**Dosages**

Drug	Dosage	Combinations available (Calcium Channel Blocker/Angiotensin Modulator)
amlodipine/benazepril (Lotrel) <sup>59</sup>	1 daily	2.5/10, 5/10, 5/20, 10/20 mg capsules Brand only – 5/40, 10/40 mg capsules
amlodipine/olmesartan (Azor) <sup>60</sup>	1 daily	5/20, 5/40, 10/20, 10/40 mg tablets
amlodipine/telmisartan (Twynsta) <sup>61</sup>	1 daily	5/40 mg, 10/40 mg, 5/80 mg, 10/80 mg
amlodipine/valsartan (Exforge) <sup>62</sup>	1 daily	5/160, 10/160, 5/320, 10/320 mg tablets
amlodipine/valsartan/HCTZ (Exforge HCT) <sup>63</sup>	1 daily	5/160/12.5, 10/160/12.5, 5/160/25, 10/160/25, 10/320/25 mg tablets
valsartan/aliskiren (Valturna) <sup>64</sup>	1 daily	160/150, 320/300
verapamil SR/trandolapril (Tarka) <sup>65</sup>	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/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.<sup>66</sup> 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  $\geq 95$  mm Hg and  $\leq 120$  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.<sup>67</sup> 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.<sup>68</sup>

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.<sup>69</sup> Patients underwent a two-week washout period and then started on benazepril 40 mg daily. Patients with a mean sitting DBP  $\geq 95$  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.<sup>70</sup> 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.<sup>71</sup>

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).<sup>72</sup> 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.<sup>73</sup> 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.<sup>74</sup> 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 mmHg; DBP: -9.2 mm Hg versus -11.3 mmHg; both  $p = \text{NS}$ ). Safety profiles did not differ between groups, but cough was more common in the combination group (11.0 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.<sup>75</sup> In a randomized, double-blind trial, the baseline characteristics of the two groups were similar with mean body mass index (BMI) of 31 kg/m<sup>2</sup> and 60 percent of patients had a diagnosis of diabetes.<sup>76</sup> 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.<sup>77</sup> The combination of amlodipine/benazepril was superior to the benazepril-hydrochlorothiazide 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.<sup>78</sup> 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.<sup>79</sup> 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 ( $20 \pm 0.7$  versus  $17.5 \pm 0.7$  mm Hg,  $p = 0.0003$  and  $11.6 \pm 0.4$  versus  $10.4 \pm 0.4$  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.<sup>80</sup> After a washout period followed by a single-blind valsartan 160 mg run-in period, patients with mean sitting DBP  $\geq 90$  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  $\geq 10$  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.<sup>81</sup> 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 mmHg 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  $\geq 160$  mmHg and  $<200$  mmHg) were randomized to receive either combination amlodipine/valsartan or amlodipine monotherapy for eight weeks.<sup>82</sup> 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 mmHg in favor of the combination product.

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

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.<sup>83</sup> 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.<sup>84</sup> 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.<sup>85,86</sup>

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.<sup>87</sup> 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.<sup>88</sup> 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.<sup>89</sup> 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.<sup>90</sup> 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.<sup>91</sup> 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 alone<sup>92</sup>. 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.<sup>93</sup> 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/telmisartan (Twynsta) 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).<sup>94</sup> 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).

Patients ( $n=1,078$ ) with a DBP  $\geq 100$  mm Hg at baseline were included in a subgroup analysis of the above study.<sup>95</sup> 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.<sup>96</sup> 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.

### valsartan/aliskiren (Valturna)

A double-blind study was conducted to the maximum recommended doses of aliskiren and valsartan compared with each drug alone in 1,797 patients with hypertension.<sup>97</sup> Patients with a mean sitting DBP 95-109 mm Hg and eight-hour daytime ambulatory diastolic blood pressure  $\geq 90$  mm Hg were randomized to receive aliskiren 150 mg ( $n=437$ ), valsartan 160 mg ( $n=455$ ), aliskiren 150 mg plus valsartan 160 mg ( $n=446$ ), or placebo ( $n=459$ ) for four weeks. After four weeks, doses were forced titrated to the maximum recommended dose (aliskiren 300 mg and valsartan 320 mg) for an additional four weeks of therapy. The change in mean sitting DBP from baseline to week eight was the primary endpoint. At week eight, aliskiren 300 mg plus valsartan 320 mg lowered mean sitting DBP from baseline by 12.2 mm Hg, significantly more than either monotherapy (aliskiren 300 mg;  $-9$  mm Hg,  $p < 0.0001$ ; valsartan 320 mg;  $-9.7$  mm Hg,  $p < 0.0001$ ), or with placebo ( $-4.1$  mm Hg,  $p < 0.0001$ ). Adverse events were similar in all groups.



aliskiren (Tekturna), valsartan (Diovan), valsartan/HCTZ (Diovan HCT), and aliskiren/valsartan (Valturna)

A multicenter, placebo-controlled, eight-week trial evaluated aliskiren and valsartan alone or in combination, and valsartan/HCTZ in 1,123 patients with mild to moderate hypertension.<sup>98</sup> Initially, patients underwent a three to four week single-blind placebo run-in and were then randomized in a modified factorial study design to receive once-daily, double-blind oral treatment with placebo, aliskiren 75, 150, or 300 mg, valsartan 80, 160, or 320 mg, aliskiren and valsartan in combination, or valsartan/hydrochlorothiazide (160/12.5 mg). The primary efficacy end point was the change from baseline in mean sitting DBP. Aliskiren 300 mg significantly lowered mean sitting DBP and SBP compared with placebo ( $p < 0.0001$ ). Aliskiren monotherapy demonstrated safety and tolerability profiles comparable to placebo. Changes in DBP and SBP were fitted to a first-order dose-response surface (lack-of-fit test,  $p = 0.65$ ), which showed that aliskiren and valsartan alone and in combination produced dose-related reductions in DBP and SBP. Coadministration of aliskiren and valsartan produced a greater antihypertensive effect than either drug alone, comparable in magnitude to the effect of valsartan/hydrochlorothiazide, with similar tolerability to the component monotherapies and to placebo.

### 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 direct 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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