


Department of Vermont Health Access

***Therapeutic Class Review
Renin Inhibitors***

Overview/Summary

Aliskiren (Tekturna[®]) is the only single entity direct renin inhibitor available in the United States (U.S.). It is Food and Drug Administration (FDA) approved for the treatment of hypertension, either as monotherapy or in combination with other antihypertensive agents.¹ It has been used off-label for the treatment of proteinuria in patients with type 2 diabetes mellitus and nephropathy despite optimized renoprotective therapy.² Currently, no generic product is available.

There are four combination renin inhibitor products available in the U.S. which combines the direct renin inhibitor aliskiren with other blood pressure-lowering medications from different therapeutic classes including thiazide diuretics, calcium channel blockers and angiotensin receptor blockers. The products currently available include aliskiren/amlodipine (Tekamlo[®]), aliskiren/amlodipine/hydrochlorothiazide (Amturnide[®]), aliskiren/hydrochlorothiazide (Tekturna HCT[®]) and aliskiren/valsartan (Valturna[®]). These agents are FDA approved for the treatment of hypertension. Currently, no combination renin inhibitor is available generically.

The renin-angiotensin-aldosterone system (RAAS) is the most important component in the homeostatic regulation of blood pressure.³ Renin catalyzes the conversion of angiotensinogen to angiotensin I, which is the first and rate-limiting step of the RAAS.³⁻⁵ Angiotensin I is then cleaved to angiotensin II by angiotensin-converting enzyme. Angiotensin II can increase blood pressure by direct vasoconstriction and stimulation of catecholamine release. In addition, angiotensin II induces aldosterone secretion, leading to sodium and fluid retention.⁵ Angiotensin II exerts other detrimental cardiovascular effects including hypertrophy, inflammation, remodeling and thrombosis. Through a negative feedback mechanism, angiotensin II inhibits renin release. As a direct renin inhibitor, aliskiren reduces angiotensin I, angiotensin II and aldosterone levels by binding to renin with high affinity in the plasma.¹ All drugs that inhibit the RAAS, including aliskiren, can suppress the negative feedback loop and cause a compensatory increase in plasma renin concentrations. Aliskiren blocks the effects of increased renin levels. The effects of aliskiren on other components of the RAAS are not known.

Amlodipine, a nondihydropyridine calcium channel blocker inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Cardiac and vascular smooth muscle contraction depends on the movement of extracellular calcium ions into cells through specific ion channels. Amlodipine inhibits calcium ion influx and exerts a greater effect on vascular smooth muscle cells compared to cardiac muscle cells. Amlodipine is a peripheral arterial vasodilator, which results in a reduction in peripheral vascular resistance and reduction in blood pressure.⁶

Hydrochlorothiazide, a thiazide diuretic, increases the excretion of sodium and chloride by inhibiting their reabsorption in the ascending loop of Henle and the early distal tubules of the kidney. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, which increases plasma renin activity, aldosterone secretion and subsequently potassium excretion in the urine. The exact antihypertensive mechanism of the thiazide diuretics is unknown, although sodium depletion appears to be an important factor.⁶

Valsartan produces its antihypertensive effects by blocking the effects of angiotensin II. This is accomplished by selectively blocking the binding of angiotensin II to the AT₁ receptor in tissues including

vascular smooth muscle and the adrenal gland. Its mechanism of action is not dependent on the synthesis of angiotensin II.⁶

The European Society of Hypertension/European Society of Cardiology 2009 Reappraisal of Guidelines on Hypertension Management concludes that the use of aliskiren in the treatment of hypertension is justified based on available evidence, particularly when used in combination with other agents.⁷ The completion of ongoing trials with hard endpoints evaluating the use of aliskiren as monotherapy and in combination with other agents will further define the role of aliskiren in the treatment of hypertension. No other clinical guideline addresses the use of aliskiren.

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Single Entity Agents		
Aliskiren (Tekturna [®])	Renin inhibitor	-
Combination Products		
Aliskiren/amlodipine (Tekamlo [®])	Renin inhibitor/calcium channel blocker	-
Aliskiren/amlodipine/hydrochlorothiazide (Amturnide [®])	Renin inhibitor/calcium channel blocker/thiazide diuretic	-
Aliskiren/hydrochlorothiazide (Tekturna HCT [®])	Renin inhibitor/thiazide diuretic	-
Aliskiren/valsartan (Valturna [®])	Renin inhibitor/angiotensin receptor blocker	-

Indications

Table 2. Food and Drug Administration (FDA) Approved Indications^{1,8-11}

Generic Name	Treatment of Hypertension Either Alone or in Combination with Other Antihypertensive Agents	Treatment of Hypertension; Not as Initial Therapy	Treatment of Hypertension as Initial Therapy in Patients Likely to Need Multiple Drugs to Achieve Blood Pressure Goals	Treatment of Hypertension in Patients Not Adequately Controlled With Monotherapy	Treatment of Hypertension as a Substitute for its Titrated Components
Single Entity Agents					
Aliskiren	✓				
Combination Products					
Aliskiren/ amlodipine			✓	✓	✓
Aliskiren/ amlodipine/ hydrochlorothiazide		✓			
Aliskiren/ hydrochlorothiazide			✓	✓	
Aliskiren/ valsartan			✓	✓	✓

Pharmacokinetics

The pharmacokinetic properties of the single entity rennin inhibitors and the individual components of the combination rennin inhibitors are outlined in table 3.

Table 3. Pharmacokinetics^{1,8-15}

Generic Name	Bioavailability (%)	Protein Binding (%)	Metabolism	Active Metabolites	Renal Excretion (%)	Half-Life (hours)
Aliskiren	2.5	47 to 51	Liver	Unknown	0.6	24
Amlodipine	64 to 90	93	Liver	No	70	30 to 60
Hydrochlorothiazide	Not reported	68	Not metabolized	No	Not reported	5.8 to 18.9
Valsartan	10 to 35	95	Liver	No	13	12

Clinical Trials

Limited comparative trials of aliskiren with other antihypertensive agents, including the angiotensin-converting enzyme inhibitors¹⁶ and angiotensin receptor blockers¹⁷⁻¹⁹ have generally demonstrated similar efficacy when administered in comparable doses. In general, the incidence of side effects was also comparable. One study reported better efficacy with aliskiren compared to ramipril, and a higher incidence of cough with ramipril (5.5%) compared to aliskiren (2.1%).²⁰ Schmieder et al compared monotherapy with aliskiren to monotherapy with hydrochlorothiazide and demonstrated significantly lower systolic and diastolic blood pressures at weeks six and 12 with aliskiren in addition to better overall response rates, however the significant difference in systolic blood pressure was not maintained at week 52.²¹

Clinical trials have evaluated the use of aliskiren in combination with amlodipine, hydrochlorothiazide and valsartan in the treatment of hypertension. In general, the combination groups showed significantly greater blood pressure-lowering efficacy compared to monotherapy with each individual agent or placebo.²²⁻²⁷ Drummond et al compared daily aliskiren/amlodipine 150/5 mg to monotherapy with amlodipine 5 or 10 mg daily in patients not fully responding to monotherapy with amlodipine 5 mg daily. Significant reductions in systolic and diastolic blood pressure were observed when comparing the combination therapy to amlodipine 5 mg, though no significant difference was observed between the combination therapy and amlodipine 10 mg. Thus, combination therapy was as effective as dose titration to amlodipine 10 mg daily in those not responding to therapy with amlodipine 5 mg. Similar results were observed in the proportion of patients responding to treatment and the proportion of patients achieving blood pressure control.²⁸

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Oh et al²⁹</p> <p>Aliskiren 150, 300 or 600 mg Daily</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, PG, RCT</p> <p>Men and women 18 years of age and older with mild-to-moderate essential hypertension (DBP ≥95 and <110 mm Hg)</p>	<p>N=672</p> <p>8 weeks</p>	<p>Primary: Change in mean sitting DBP</p> <p>Secondary: Change in mean sitting SBP, 24-hour ABPM, proportion achieving a successful treatment response (defined as DBP <90 mm Hg or a ≥10 mm Hg pressure reduction from baseline) or BP control (defined as <140/90 mm Hg), plasma renin activity and concentration, safety and tolerability</p>	<p>Primary: All three doses investigated provided significantly greater reductions in mean sitting DBP from baseline compared to placebo ($P<0.0001$). The mean sitting DBP reductions were 10.3 mm Hg with 150 mg, 11.1 mm Hg with 300 mg and 12.5 mm Hg with 600 mg compared to 4.9 mm Hg with placebo.</p> <p>Secondary: All three doses provided significantly greater reductions in mean sitting SBP from baseline compared to placebo ($P<0.0001$). The mean sitting SBP reductions were 13.0 mm Hg with 150 mg, 14.7 mm Hg with 300 mg and 15.8 mm Hg with 600 mg compared to 3.8 mm Hg with placebo.</p> <p>Reduction in the 24-hour ABPM was significantly greater in all doses of aliskiren compared to placebo ($P<0.0001$). Reductions in mean ambulatory DBP and SBP were consistent across the 24-hour dosing interval with all aliskiren doses.</p> <p>The proportion of patients achieving a successful treatment response was 59.3% with 150 mg, 63.3% with 300 mg and 69.3% with 600 mg compared to 36.2% with placebo ($P<0.0001$).</p> <p>The proportion of patients achieving BP control was 35.9% with 150 mg, 41.6% with 300 mg and 46.4% with 600 mg compared to 20.3% with placebo ($P<0.0001$).</p> <p>Plasma renin activity decreased 79.5% with 150 mg, 81.1% with 300 mg and 75.0% with 600 mg compared to an increase of 19.5% with placebo (P values not reported). Aliskiren treatment for eight weeks resulted in dose-dependent increases from baseline in renin concentrations (51.5, 101.6, and 228.5% for 150, 300 and 600 mg, respectively; P values not reported). In the placebo group, renin concentrations were almost unchanged.</p> <p>In general, aliskiren was well tolerated. The incidence of adverse events with aliskiren 150, 300 and 600 mg was 40.1, 46.7 and 52.4%, respectively, compared to 43.0% for placebo. The incidence of diarrhea was significantly higher with 600 mg (11.4%; $P<0.0001$) compared to 300 mg (1.8%), 150 mg (1.2%) and placebo (1.2%).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Kushiro et al¹⁷</p> <p>Aliskiren 75, 150 or 300 mg Daily</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, PG, RCT</p> <p>Japanese men and women between the ages of 20 and 80 with essential hypertension (mean sitting DBP of ≥ 90 and < 110 mm Hg during the run-in period and ≥ 95 and < 110 mm Hg at baseline)</p>	<p>N=455</p> <p>8 weeks (active treatment)</p>	<p>Primary: Change in mean sitting DBP</p> <p>Secondary: Change in mean trough sitting SBP, proportion of patients responding to treatment (mean sitting DBP < 90 mm Hg and/or a ≥ 10 mm Hg decrease in mean sitting DBP from baseline), dose-response relationship, and safety</p>	<p>Primary: All three aliskiren doses provided significantly greater reductions in mean sitting DBP from baseline compared to placebo. The placebo-corrected reductions in mean sitting DBP were 4.0 mm Hg with 75 mg, 4.5 mm Hg with 150 mg and 7.5 mm Hg with 300 mg ($P < 0.0005$).</p> <p>Secondary: The mean sitting SBP reductions were significantly lower with all aliskiren doses when compared to placebo. The placebo-corrected reductions in mean sitting SBP were 5.7 mm Hg with 75 mg, 5.9 mm Hg with 150 mg and 11.2 mm Hg with 300 mg ($P < 0.001$).</p> <p>The proportion of responders at study end point was 47.8% with 75 mg, 48.2% with 150 mg and 63.7% with 300 mg compared to 27.8% with placebo ($P < 0.005$).</p> <p>Dose-response analysis showed that the relationship between reductions in mean sitting DBP and SBP and aliskiren dose was almost linear. However, further analyses revealed that a pattern of similar reductions with 75 and 150 mg and greater reductions with 300 mg was a better fit for both mean sitting DBP and SBP.</p> <p>The incidence of drug-related adverse events was comparable between aliskiren (53 to 55%) and placebo (50%). There was no evidence of a dose-dependent increase in the incidence of all-causality adverse events at the aliskiren doses evaluated in this study.</p>
<p>Musini et al¹⁸</p> <p>Aliskiren 75, 150, 300 or 600 mg</p> <p>vs</p> <p>placebo</p>	<p>MA</p> <p>Patients 18 years of age and older with mild to moderate hypertension</p>	<p>N=3,694</p> <p>Varying duration (2 to 4 week run-in period, 4-8 week treatment period)</p>	<p>Primary: Change from baseline in trough and/or peak SBP and DBP compared to placebo</p> <p>Secondary: Change in standard deviation compared to placebo, change</p>	<p>Primary: Aliskiren was "superior" to placebo in lowering mean sitting SBP and DBP (P value not reported).</p> <p>Secondary: End of treatment standard deviation was similar in the placebo and aliskiren arms.</p> <p>No data were provided at the week eight endpoint for change in heart rate.</p> <p>No trials reported on pulse pressure at baseline or endpoint.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			in pulse pressure, change in heart rate, number of withdrawals due to adverse effects, and number of patients with dry cough or angioedema	<p>No significant difference between aliskiren and placebo was observed in withdrawals due to adverse events.</p> <p>No trials reported on angioedema. One trial reported on dry cough, with two in the placebo group (1.1%), two in the 75 mg group (1.1%), five in the 150 mg group (2.8%) and one in the 300 mg group (0.6%).</p> <p>No difference was observed in reduction in trough SBP and DBP between 150 and 75 mg or between 600 and 300 mg. 300 mg significantly lowered SBP and DBP compared to 150 mg.</p>
<p>Schmieder et al²¹</p> <p>Aliskiren 150 mg Daily then 300 mg Daily after 3 weeks</p> <p>vs</p> <p>HCTZ 12.5 mg Daily then 25 mg Daily after 3 weeks</p> <p>vs</p> <p>placebo, then either aliskiren 300 mg Daily or HCTZ 25 mg Daily after 6 weeks</p>	<p>AC, DB, PG, RCT</p> <p>Patients 18 years of age and older with essential hypertension, a mean sitting DBP ≥ 90 and < 110 mm Hg; at randomization, patients had to have a mean sitting DBP ≥ 95 and < 110 mm Hg and show a difference of ≤ 10 mm Hg since the previous visit</p>	<p>N=1,124</p> <p>52 weeks</p>	<p>Primary: Mean sitting DBP</p> <p>Secondary: Mean sitting SBP at week 26, mean sitting DBP and SBP at week 52, proportion of patients with response to treatment, BP control at weeks 26 and 52, and safety</p>	<p>Primary: At week six, both aliskiren and HCTZ were “superior” to placebo in lowering mean sitting DBP ($P < 0.0001$ and $P < 0.05$ respectively).</p> <p>At week 12, aliskiren was statistically “superior” to HCTZ in reducing mean sitting DBP ($P < 0.001$).</p> <p>Secondary: At week six, both aliskiren and HCTZ were “superior” to placebo in lowering mean sitting SBP ($P < 0.0001$).</p> <p>At week 12, aliskiren was statically “superior” to HCTZ in reducing mean sitting SBP ($P < 0.001$).</p> <p>Aliskiren provided a significantly greater BP response and BP control rates compared to HCTZ ($P < 0.001$).</p> <p>At week 26, 46.4% of aliskiren patients and 53.0% of HCTZ patients required additional therapy with amlodipine. Similar results were seen at week 52 ($P = 0.119$).</p> <p>At week 26, aliskiren provided statistically “superior” reductions in mean sitting SBP and DBP compared to the HCTZ regimen ($P < 0.05$ and $P < 0.01$ respectively).</p> <p>At week 52, the statistically “superior” reduction in mean sitting DBP was maintained with aliskiren compared to HCTZ ($P < 0.05$) but no significant difference</p>

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				<p>between the groups was observed at week 52 in mean sitting SBP.</p> <p>Responder rates were significantly higher with aliskiren compared to HCTZ at week 26 and week 52 ($P<0.05$ and $P<0.01$ respectively).</p> <p>The proportion of patients experiencing adverse effects was similar between groups.</p>
<p>Schmieder et al¹⁹</p> <p>Aliskiren 150 mg Daily then 300 mg Daily after 3 weeks</p> <p>vs</p> <p>HCTZ 12.5 mg Daily then 25 mg Daily after 3 weeks</p> <p>vs</p> <p>placebo, then either aliskiren 300 mg Daily or HCTZ 25 mg Daily after 6 weeks</p> <p>Subgroup analysis of Schmieder et al²¹ in obese patients.</p>	<p>AC, DB, PG, RCT</p> <p>Patients 18 years of age and older with essential hypertension, a mean sitting DBP ≥ 90 and <110 mm Hg; at randomization, patients had to have a mean sitting DBP ≥ 95 and <110 mm Hg and show a difference of ≤ 10 mm Hg since the previous visit</p>	<p>N=1,124</p> <p>52 weeks</p>	<p>Primary: Mean sitting DBP</p> <p>Secondary: Mean sitting SBP at week 26, mean sitting DBP and SBP at week 52, proportion of patients with response to treatment, BP control at weeks 26 and 52, and safety</p>	<p>Primary: The least squares mean DBP and SBP reductions at week 12 were significantly greater with aliskiren compared to HCTZ ($P<0.0001$ and $P=0.001$ respectively).</p> <p>Secondary: At week 52, aliskiren resulted in significantly greater mean sitting DBP reductions compared to HCTZ ($P<0.001$).</p> <p>BP response rates were significantly greater with aliskiren compared to HCTZ at both week 12 and week 52 ($P<0.05$).</p> <p>Significantly more obese patients achieved BP control with aliskiren compared to HCTZ at week 12 ($P=0.0013$). BP control rates were similar between groups at week 52 (P value not reported).</p>
<p>Persson et al³⁰</p> <p>Aliskiren 300 mg Daily</p> <p>vs</p> <p>irbesartan 300 mg Daily</p>	<p>DB, RCT, XO</p> <p>Adult patients with hypertension, type 2 diabetes and albuminuria</p>	<p>N=26</p> <p>Four 2 month XO treatment periods</p>	<p>Primary: Albuminuria</p> <p>Secondary: 24-hour BP, glomerular filtration rate, biomarkers,</p>	<p>Primary: Treatment with aliskiren, irbesartan and combination therapy resulted in a significant reduction in albuminuria compared to placebo ($P<0.001$). No significant difference was observed between the aliskiren and irbesartan groups.</p> <p>Combination therapy reduced albuminuria significantly more compared to placebo and either monotherapy group ($P\leq 0.028$).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>vs</p> <p>aliskiren 300 mg Daily plus irbesartan 300 mg Daily</p> <p>vs</p> <p>placebo</p>	(>100 mg/day)		and renin angiotensin-aldosterone system components	<p>Secondary:</p> <p>Systolic/diastolic 24-hour BP was significantly reduced in all treatment groups compared to placebo ($P \leq 0.009$). No significant difference was observed between the irbesartan and combination therapy group.</p> <p>Glomerular filtration rate was significantly reduced in all treatment groups compared to placebo ($P \leq 0.037$). No significant difference was observed between the irbesartan and combination therapy group.</p> <p>Aliskiren significantly reduced high-sensitivity plasma renin activity, angiotensin I and angiotensin II compared to placebo ($P < 0.001$). Irbesartan had the opposite effect. The combination of aliskiren and irbesartan counteracted the activating effects of irbesartan.</p>
<p>Strasser et al³¹</p> <p>Aliskiren 150 to 300 mg Daily</p> <p>vs</p> <p>lisinopril 20 to 40 mg Daily</p> <p>HCTZ may be added to aliskiren 300 mg or lisinopril 40 mg if additional BP control was required.</p> <p>The study did not specifically analyze the effects of HCTZ on either treatment regimen.</p>	<p>AC, DB, DD, MC, PG, RCT</p> <p>Men and women with uncomplicated severe hypertension (mean sitting DBP 105 to 119 mm Hg)</p>	<p>N=183</p> <p>8 weeks</p>	<p>Primary:</p> <p>Safety</p> <p>Secondary:</p> <p>Change in mean sitting DBP and SBP and percentage of responders</p>	<p>Primary:</p> <p>Both active treatments were well tolerated with an incidence of adverse events of 32.8% with aliskiren and 29.3% with lisinopril. The proportion of patients discontinuing treatment due to adverse events was 3.2% with aliskiren and 3.4% with lisinopril. The most frequently reported adverse events in both groups were headache, nasopharyngitis and dizziness (no <i>P</i> values were reported for this endpoint).</p> <p>Secondary:</p> <p>Aliskiren showed similar reductions from baseline to lisinopril in mean sitting DBP (-18.5 vs -20.1 mm Hg) and SBP (-20.0 vs -22.3 mm Hg; no <i>P</i> values were reported).</p> <p>Responder rates were 81.5% with aliskiren and 87.9% with lisinopril. Approximately half of patients required the addition of HCTZ to achieve BP control (53.6% with aliskiren and 44.8% with lisinopril; no <i>P</i> values were reported).</p>
Duprez et al ¹⁶	AC, DB, PG,	N=901	Primary:	Primary:

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(abstract) Aliskiren 150 to 300 mg Daily vs ramipril 5 to 10 mg Daily HCTZ 12.5 to 25 mg Daily was allowed as add-on therapy at week 12 and amlodipine 5 to 10 mg Daily at week 22.	RCT Patients 65 years of age and older with SBP \geq 140 mm Hg	36 weeks	Mean sitting SBP at week 12 Secondary: Mean sitting DBP, BP control, and patients requiring add-on therapy with HCTZ or amlodipine	Aliskiren therapy was found non-inferior to ramipril therapy in mean sitting SBP ($P<0.001$). Aliskiren therapy was found to be “superior” to ramipril therapy in reduction in mean sitting SBP ($P=0.02$). Secondary: Aliskiren therapy was found non-inferior to ramipril therapy in mean sitting DBP ($P<0.001$). Aliskiren therapy was found to be “superior” to ramipril therapy in reduction in mean sitting DBP ($P<0.01$). Significantly more patients achieved BP control with aliskiren therapy compared to ramipril therapy ($P<0.01$). At week 36, significantly fewer patients required add-on therapy with HCTZ or amlodipine ($P=0.01$ and $P=0.048$ respectively).
Andersen et al ²⁰ Aliskiren 150 to 300 mg Daily vs ramipril 5 to 10 mg Daily The addition of HCTZ was permitted at week 12 in patients not achieving adequate BP control (<140/90 mm Hg). The study did not specifically analyze the effects of HCTZ on either treatment regimen.	AC, DB, MC, PC, RCT Men and women 18 years of age and older with essential hypertension (mean sitting DBP 90 to 109 mm Hg)	N=842 26 weeks (active treatment)	Primary: Change in mean sitting DBP at week 26 Secondary: Change in mean sitting SBP at week 26, change in mean sitting SBP and DBP at weeks six and 12 (comparing aliskiren and ramipril monotherapy), proportion achieving BP control (<140/90 mm Hg), proportion achieving SBP control (<140 mm	Primary: Reductions in mean sitting DBP at week 26 were significantly greater with aliskiren-based therapies (-13.2 mm Hg) than with ramipril-based therapies (-12.0 mm Hg; $P=0.0250$). Secondary: Reductions in mean sitting SBP at week 26 were significantly greater with aliskiren-based therapies (-17.9 mm Hg) than with ramipril-based therapies (-15.2 mm Hg; $P=0.0036$). Mean changes in sitting SBP were significantly greater with aliskiren-based therapies (-12.9 and -14.0 mm Hg, respectively) than ramipril-based therapies (-10.5 and -11.3 mm Hg, respectively) at weeks six and 12 ($P=0.0041$ and $P=0.0027$, respectively). Mean changes in sitting DBP were not significantly greater with aliskiren-based therapies (-10.5 and -11.3 mm Hg, respectively) than ramipril-based therapies (-9.5 and -9.7 mm Hg, respectively) at week six but were significantly greater at week 12 ($P=0.0689$ and $P=0.0056$, respectively). The proportion of patients achieving overall BP control <140/90 mm Hg was significantly higher with aliskiren-based therapy (61.4%) than with ramipril-based

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			Hg), and safety	<p>therapy (53.1%; $P=0.0205$) at week 26. Also, the proportion of patients achieving SBP control <140 mm Hg was significantly higher with aliskiren-based therapy (72.5%) than with ramipril-based therapy (64.1%; $P=0.0075$) at week 26.</p> <p>The majority of adverse events reported during the active treatment period were mild or moderate in intensity and transient. Most events occurred at a similar incidence in the two groups with the exception of cough which was considered treatment-related in 5.5% of patients receiving ramipril-based therapies vs 2.1% of patients receiving aliskiren-based therapies (no P values reported).</p>
<p>Gradman et al³²</p> <p>Aliskiren 150, 300, or 600 mg Daily</p> <p>vs</p> <p>irbesartan 150 mg Daily</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, PG, RCT</p> <p>Men and women, 18 years of age or older, with mild-to-moderate essential hypertension (mean sitting DBP ≥ 95 and <110 mm Hg)</p>	<p>N=652</p> <p>13 weeks (8 weeks active treatment)</p>	<p>Primary: Change in mean sitting DBP and SBP</p> <p>Secondary: Proportion of patients achieving BP control (<140/90 mm Hg), and safety</p>	<p>Primary: Decreases in mean sitting DBP at eight weeks were significantly greater with all doses of aliskiren compared to placebo ($P<0.001$). The least-squares mean reductions in trough DBP for aliskiren 150, 300 and 600 mg were 9.3, 11.8, and 11.5 mm Hg, respectively, vs 6.3 mm Hg for placebo.</p> <p>Decreases in mean sitting SBP at eight weeks were significantly greater with all doses of aliskiren compared to placebo ($P<0.001$). The least-squares mean reductions in trough SBP for aliskiren 150, 300 and 600 mg were 11.4, 15.8, and 15.7 mm Hg, respectively, vs 5.3 mm Hg for placebo.</p> <p>The antihypertensive effect of aliskiren 150 mg was comparable to irbesartan 150 mg with reductions of 8.9 and 12.5 mm Hg for mean sitting DBP and SBP, respectively. Aliskiren 300 and 600 mg produced significantly greater mean sitting DBP reductions than irbesartan 150 mg ($P<0.05$). While the reductions in mean sitting SBP were greater with aliskiren 300 and 600 mg than irbesartan 150 mg, these differences were not statistically significant (P values not reported).</p> <p>Secondary: The percentage of patients achieving BP control was significantly greater with all doses of aliskiren (37.8%, 150 mg; 50.0%, 300 mg; 45.7%, 600 mg) and irbesartan (33.8%) compared to placebo (20.8%; $P<0.05$). More patients on aliskiren 300 and 600 mg achieved BP control compared to irbesartan ($P<0.05$).</p> <p>Drug-related adverse events for both aliskiren and irbesartan were comparable to placebo and the most commonly reported adverse events were headache, dizziness, and diarrhea. The number of patients discontinuing therapy was similar</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				in all groups.
<p>Stanton et al³³</p> <p>Aliskiren 37.5, 75, 150, or 300 mg Daily</p> <p>vs</p> <p>losartan 100 mg Daily</p>	<p>AC, DB, MC, PG, RCT</p> <p>Men and women 21 to 70 years of age with mild-to-moderate hypertension (SBP ≥140 mm Hg)</p>	<p>N=226</p> <p>4 weeks</p>	<p>Primary: Change in daytime ambulatory SBP</p> <p>Secondary: Changes in clinic SBP and DBP, plasma renin activity, plasma aliskiren levels, and adverse events</p>	<p>Primary: A clear dose-dependent reduction in daytime ambulatory SBP was observed with increasing aliskiren doses (with mean changes of -0.40 mm Hg with aliskiren 37.5 mg, -5.3 mm Hg with aliskiren 75 mg, -8.0 mm Hg with aliskiren 150 mg, and -11.0 mm Hg with aliskiren 300 mg; <i>P</i>=0.0002). The change in daytime SBP with losartan (-10.9 mm Hg) was significantly different than aliskiren 37.5 mg but not the other higher aliskiren dosages (<i>P</i> values not reported).</p> <p>Secondary: Clinic SBP and DBP, both in the sitting and standing positions, decreased with aliskiren in a dose-dependent manner, whereas heart rate was unaltered. The decreases in clinic BPs were similar for losartan and aliskiren 150 and 300 mg.</p> <p>Dose-dependent reductions in plasma renin activity were also observed (median change: 55, 60, 77 and 83% with 37.5, 75, 150 and 300 mg aliskiren, respectively; <i>P</i>=0.0008). By contrast, plasma renin activity increased by 110% with losartan.</p> <p>Rate of adverse events was 22% with aliskiren 37.5 mg, 35% with aliskiren 75 mg, 25% with aliskiren 150 mg, 23% with aliskiren 300 mg, and 32% with losartan (no <i>P</i> value reported). There was no increase in the number of adverse events when increasing the dose of aliskiren.</p>
<p>Wiysonge et al³⁴</p> <p>Other antihypertensive therapies (i.e., placebo, diuretics, calcium channel blockers or renin-angiotensin system inhibitors)</p> <p>vs</p> <p>β-blockers (atenolol, metoprolol, oxprenolol)*</p>	<p>MA</p> <p>13 RCTs evaluating patients ≥18 years of age with hypertension</p>	<p>N=91,561</p> <p>Duration varied</p>	<p>Primary: All-cause mortality</p> <p>Secondary: Stroke, coronary heart disease, cardiovascular death, total cardiovascular disease, adverse reactions</p>	<p>Primary: There was not a significant difference observed in all-cause mortality between β-blocker therapy and placebo (RR, 0.99; 95% CI, 0.88 to 1.11; <i>P</i> value not reported), diuretics (RR, 1.04; 95% CI, 0.91 to 1.19; <i>P</i> value not reported) or renin-angiotensin system inhibitors (RR, 1.10; 95% CI, 0.98 to 1.24; <i>P</i> value not reported). There was a significantly higher rate in all-cause mortality with β-blocker therapy compared to calcium channel blockers (RR, 1.07; 95% CI, 1.00 to 1.14; <i>P</i>=0.04).</p> <p>Secondary: There was a significant decrease in stroke observed with β-blocker therapy compared to placebo (RR, 0.80; 95% CI, 0.66 to 0.96). Also there was a significant increase in stroke with β-blocker therapy compared to calcium channel blockers</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
or propranolol)				<p>(RR, 1.24; 95% CI, 1.11 to 1.40) and renin-angiotensin system inhibitors (RR, 1.30; 95% CI, 1.11 to 1.53), but there was no difference observed compared to diuretics (RR, 1.17; 95% CI, 0.65 to 2.09).</p> <p>Coronary heart disease risk was not significantly different between β-blocker therapy and placebo (RR, 0.93; 95% CI, 0.81 to 1.07), diuretics (RR, 1.12; 95% CI, 0.82 to 1.54), calcium channel blockers (RR, 1.05; 95% CI, 0.96 to 1.15) or renin-angiotensin system inhibitors (RR, 0.90; 95% CI, 0.76 to 1.06).</p> <p>The risk of total cardiovascular disease was lower with β-blocker therapy compared to placebo (RR, 0.88; 95% CI, 0.79 to 0.97). The effect of β-blocker therapy on cardiovascular disease was significantly worse than that of calcium channel blockers (RR, 1.18; 95% CI, 1.08 to 1.29), but was not significantly different from that of diuretics (RR, 1.13; 95% CI, 0.99 to 1.28) or renin-angiotensin system inhibitors (RR, 1.00; 95% CI, 0.72 to 1.3).</p> <p>There was a significantly higher rate of discontinuation due to side effects with β-blocker therapy compared to diuretics (RR, 1.86; 95% CI, 1.39 to 2.50) and renin-angiotensin system inhibitors (RR, 1.41; 95% CI, 1.29 to 1.54), but there was no significant difference compared to calcium channel blockers (RR, 1.20; 95% CI, 0.71 to 2.04). Actual side effects were not reported.</p>
<p>Parving et al³⁵ (AVOID)</p> <p>Losartan 100 mg daily plus aliskiren 150 mg daily for 3 months then 300 mg for an additional 3 months</p> <p>vs</p> <p>losartan 100 mg plus placebo</p>	<p>DB, MC, PC, RCT</p> <p>Hypertensive patients who were 18 to 85 years of age with type 2 diabetes and nephropathy</p>	<p>N=599</p> <p>6 months</p>	<p>Primary: Reduction in albumin:creatinine ratio at six months</p> <p>Secondary: BP reductions and adverse events</p>	<p>Primary: Treatment with aliskiren 300 mg daily as compared to placebo reduced the mean urinary albumin:creatinine ratio by 20% (95% CI, 9 to 30; $P<0.001$), with a reduction of 50% or more in 24.7% of the patients who received aliskiren as compared to 12.5% of those who received placebo ($P<0.001$).</p> <p>Secondary: A small difference in BP was seen between the treatment groups by the end of the study period with SBP and DBP pressures 2 and 1 mm Hg lower, respectively, in the aliskiren group ($P=0.07$ and $P=0.08$, respectively).</p> <p>The total numbers of adverse and serious adverse events were similar in the groups.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Jordan et al²²</p> <p>Aliskiren 150 mg Daily</p> <p>vs</p> <p>amlodipine 5 mg Daily</p> <p>vs</p> <p>irbesartan 150 mg Daily</p> <p>vs</p> <p>placebo</p> <p>After 4 weeks, doses of aliskiren, irbesartan and amlodipine were doubled and treatment was continued for an additional 8 weeks.</p> <p>All patients continued to receive HCTZ 25 mg Daily.</p>	<p>DB, DD, MC, PG, RCT</p> <p>Obese men and women (BMI ≥ 30 kg/m²) 18 years of age and older with essential hypertension (mean sitting DBP 95 to 109 mm Hg and SBP < 180 mm Hg) who had not responded to 4 weeks of treatment with HCTZ 25 mg</p>	<p>N=489</p> <p>16 weeks (4 weeks of HCTZ monotherapy and 12 weeks of combination therapy)</p>	<p>Primary: Change in mean sitting DBP with aliskiren 300 mg plus HCTZ vs HCTZ alone at eight weeks</p> <p>Secondary: Comparisons of mean sitting DBP and SBP with aliskiren plus HCTZ vs the other treatment groups, percentage of responders (mean sitting DBP < 90 mm Hg or $\geq a$ 10 mm Hg reduction from baseline), proportion of patients achieving BP control (mean sitting BP $< 140/90$ mm Hg), plasma renin activity, safety and tolerability</p>	<p>Primary: Aliskiren 300 mg added to HCTZ 25 mg significantly reduced mean sitting DBP compared to HCTZ alone at week eight (mean difference, -4.0; $P < 0.0001$).</p> <p>Secondary: Aliskiren 300 mg added to HCTZ caused numerically larger reductions in mean sitting DBP and SBP compared to amlodipine 10 mg plus HCTZ and irbesartan 300 mg plus HCTZ at week eight, but there were no statistically significant differences between treatment groups ($P > 0.05$).</p> <p>Responder rates were significantly higher with aliskiren plus HCTZ than HCTZ alone at week eight ($P = 0.0193$) and week 12 ($P = 0.004$) but comparable to responder rates observed with amlodipine plus HCTZ ($P > 0.05$) and irbesartan plus HCTZ ($P > 0.05$).</p> <p>The proportion of patients achieving BP control was significantly higher with aliskiren plus HCTZ than HCTZ alone at week eight ($P = 0.0005$) and week 12 ($P = 0.0001$) but not statistically different than amlodipine plus HCTZ ($P > 0.05$) and irbesartan plus HCTZ ($P > 0.05$).</p> <p>Plasma renin activity significantly increased ($P < 0.05$) during four weeks of HCTZ monotherapy. Combination with aliskiren neutralized this increase and led to an overall significant reduction in plasma renin activity compared to pretreatment baseline ($P < 0.05$) whereas amlodipine and irbesartan led to further significant increases ($P < 0.05$).</p> <p>All of the study treatments were generally well tolerated. Amlodipine plus HCTZ (45.2%) was associated with a higher incidence of adverse events than the other treatment groups (36.1 to 39.3%; no P values reported), largely due to a higher rate of peripheral edema (11.1 vs 0.8 to 1.6%; no P values reported).</p>
<p>Drummond et al²⁸</p> <p>Aliskiren/amlodipine 150/5 mg Daily</p> <p>vs</p>	<p>AC, DB, MC, PG, RCT</p> <p>Patients 18 years of age and older with</p>	<p>N=545</p> <p>6 weeks</p>	<p>Primary: Change in DBP at six weeks</p> <p>Secondary: SBP, comparison</p>	<p>Primary: DBP reduction was significantly greater in the combination therapy group compared to those in the amlodipine 5 mg group ($P < 0.0001$).</p> <p>Secondary: SBP reduction was significantly greater in the combination therapy group</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
amlodipine 5 mg Daily vs amlodipine 10 mg Daily Patients not responding to amlodipine 5 mg Daily at the end of 4 week single-blind run-in period received combination therapy, continuation of amlodipine 5 mg Daily or titration to amlodipine 10 mg Daily.	mild to moderate hypertension		of SBP and DBP reductions between combination therapy group and amlodipine 10 mg group, proportion of patients responding to treatment, and proportion of patients achieving BP control	compared to those in the amlodipine 5 mg group ($P<0.0001$). No significant differences were observed in DBP or SBP reduction between the combination therapy group and the amlodipine 10 mg group ($P=0.6167$ and $P=0.2666$ respectively). The proportion of patients responding to treatment was significantly higher in the combination therapy group compared to the amlodipine 5 mg group ($P<0.0001$). No significant difference was observed between the combination therapy group and the amlodipine 10 mg group (P value not reported). The proportion of patients achieving BP control was significantly higher in the combination therapy group compared to the amlodipine 5 mg group ($P<0.0001$). No significant difference was observed between the combination therapy group and the amlodipine 10 mg group ($P=0.5229$).
Villamil et al ²³ Aliskiren 75, 150 or 300 mg Daily vs HCTZ 6.25, 12.5 or 25 mg Daily vs aliskiren plus HCTZ (every dose combination except aliskiren 300 mg and HCTZ 6.25 mg) Daily vs	DB, MC, PC, PG, RCT, factorial design Men and women 18 years of age and older with mild-to-moderate essential hypertension (mean sitting DBP 95 to 109 mm Hg)	N=2,776 8 weeks	Primary: Comparison of aliskiren to placebo on change in mean sitting DBP, comparison of aliskiren plus HCTZ to individual components on change in mean sitting DBP Secondary: Same as primary but mean sitting SBP, dose-response efficacy for all treatment groups, proportion achieving a	Primary: Aliskiren monotherapy significantly reduced mean sitting DBP ($P=0.0002$) and the reductions were dose related. Although pairwise comparisons indicated that all three doses of aliskiren were statistically more effective than placebo, after adjusting for multiple comparisons, only the aliskiren 150 and 300 mg doses were more effective than placebo ($P=0.09$ for aliskiren 75 mg). HCTZ monotherapy significantly reduced DBP from baseline ($P<0.01$ vs placebo), although no linear dose relationship was observed. All combinations were more effective than placebo ($P<0.0001$) with reductions in DBP ranging from 10.4 to 14.3 mm Hg. Most combination regimens were more effective than monotherapy with the individual components (exceptions were aliskiren 150 mg plus HCTZ 6.25 mg vs either monotherapy, and aliskiren 75 mg plus HCTZ 12.5 mg vs HCTZ monotherapy). Secondary: After eight weeks of therapy, aliskiren 150 and 300 mg regimens (both $P<0.0001$) were more effective than placebo in lowering mean sitting SBP, but the 75 mg dose was not ($P=0.151$).

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<p>placebo</p>			<p>successful response (DBP <90 mm Hg or a ≥10 mm Hg), proportion achieving BP control (<140/90 mm Hg), plasma renin activity, renin concentrations, and safety</p>	<p>Combination therapy was consistently more effective in reducing SBP than monotherapy with the individual components, with the exception of aliskiren 75 mg plus HCTZ 12.5 mg vs HCTZ monotherapy. Reductions in SBP with combination therapy ranged from 14.3 to 21.2 mm Hg.</p> <p>BP reductions were related to the doses of both aliskiren and HCTZ.</p> <p>Responder rates were significantly higher with aliskiren 300 mg (63.9%; $P=0.0005$), HCTZ 12.5 and 25 mg (60.6 and 59.0%, respectively; $P<0.02$) and all combination doses (58.4 to 80.6%; $P<0.05$) than placebo (45.8%). Responder rates for all combinations of aliskiren plus HCTZ 25 mg, and aliskiren 300 mg plus HCTZ 12.5 mg were higher than both monotherapies ($P<0.05$), while aliskiren 75 mg plus HCTZ 12.5 mg and aliskiren 150 mg plus HCTZ 12.5 mg were more effective than their respective aliskiren monotherapies ($P<0.05$).</p> <p>In the aliskiren and HCTZ monotherapy groups, only aliskiren 300 mg led to significantly greater control rates than placebo (46.7 vs 28.1%; $P=0.0001$). Control rates for all combinations, with the exception of aliskiren 75 mg plus HCTZ 6.25 mg, were higher than placebo ($P<0.02$). There was a trend towards improved control rates with combination therapy (37.4 to 59.5%) compared to aliskiren monotherapy (29.0 to 46.7%) or HCTZ monotherapy (32.5 to 37.8%). Combinations utilizing the higher doses of one or both drugs (aliskiren 75 to 300 mg with HCTZ 25 mg or aliskiren 150 to 300 mg with HCTZ 12.5 mg) yielded control rates that were significantly higher than monotherapy with either component.</p> <p>While all doses of aliskiren decreased plasma renin activity and all doses of HCTZ increased plasma renin activity, combination therapy resulted in decreased plasma renin activity of 46.1 to 63.5%. Renin concentrations increased in all monotherapy and combination regimens with the exception of HCTZ 6.25 and 12.5 mg.</p> <p>All active treatments were well tolerated with 37.3 to 39.2% of patients experiencing adverse events with aliskiren monotherapy, 38.7 to 42.0% with HCTZ monotherapy, 34.6 to 45.3% with aliskiren plus HCTZ, and 44% with placebo (no P values reported). Hypokalemia (serum potassium <3.5 mmol/L) occurred with the</p>

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				highest frequency with HCTZ 12.5 and 25 mg (3.9 and 5.2%, respectively). When administered in combination with aliskiren, the frequency of hypokalemia was 0.7 to 2.0% with HCTZ 12.5 mg and 2.2 to 3.4% with HCTZ 25 mg.
<p>Blumenstein et al³⁶ (abstract)</p> <p>Aliskiren/HCTZ 150/25 mg Daily</p> <p>vs</p> <p>aliskiren/HCTZ 300/25 mg Daily</p> <p>vs</p> <p>HCTZ 25 mg Daily</p>	<p>DB, RCT</p> <p>Patients with hypertension not responding to 4 weeks of monotherapy with HCTZ 25 mg Daily</p>	<p>N=722</p> <p>8 weeks</p>	<p>Primary: Mean sitting DBP and SBP</p> <p>Secondary: BP control rates</p>	<p>Primary: Mean sitting DBP and SBP reductions were significantly greater in both combination therapy groups compared to HCTZ monotherapy ($P<0.001$).</p> <p>Aliskiren/HCTZ 300/25 mg produced significantly greater reductions compared to the aliskiren/HCTZ 150/25 mg group ($P<0.05$).</p> <p>Secondary: Both combination treatment groups produced significantly greater BP control rates compared to HCTZ monotherapy ($P<0.001$).</p> <p>Aliskiren/HCTZ 300/25 mg produced significantly greater BP control rates compared to the aliskiren/HCTZ 150/25 mg group ($P<0.05$).</p>
<p>Geiger et al³⁷</p> <p>Aliskiren/HCTZ 150/25 mg Daily for 4 weeks then 300/25 mg Daily for 4 weeks</p> <p>vs</p> <p>valsartan/HCTZ 160/25 mg Daily for 4 weeks then 320/25 mg Daily for 4 weeks</p> <p>vs</p> <p>aliskiren/valsartan/HCTZ 150/160/25 mg Daily for 4 weeks then</p>	<p>AC, DB, PG, RCT</p> <p>Patients 18 years of age and older with mild to moderate hypertension</p>	<p>N=641</p> <p>8 weeks</p>	<p>Primary: DBP at week eight</p> <p>Secondary: SBP at week eight, changes in DBP and SBP at week four, and proportion of patients achieving BP control</p>	<p>Primary: The aliskiren/valsartan/HCTZ group showed significantly greater reductions in DBP at week eight compared to the other groups ($P<0.01$).</p> <p>Secondary: The aliskiren/valsartan/HCTZ group showed significantly greater reductions in SBP at week eight compared to the other groups ($P<0.01$).</p> <p>Both the valsartan/HCTZ and aliskiren/HCTZ groups demonstrated significantly greater DBP and SBP reductions compared to the HCTZ monotherapy group (P value not reported).</p> <p>At week eight, a significantly higher proportion of patients achieved BP control in the aliskiren/valsartan/HCTZ group compared to the other groups ($P<0.001$).</p> <p>At week four, a significantly higher proportion of patients achieved BP control in the aliskiren/valsartan/HCTZ group compared to the other groups ($P<0.05$).</p> <p>Both the aliskiren/HCTZ and valsartan/HCTZ groups demonstrated significantly</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>300/320/25 mg Daily for 4 weeks</p> <p>vs</p> <p>HCTZ 25 mg Daily for 8 weeks</p> <p>Patients not responding to HCTZ 25 mg Daily after 4 weeks were randomized to one of the above treatment regimens.</p>				<p>better rates of BP control compared to the HCTZ monotherapy group at week four and eight (<i>P</i> values not reported).</p>
<p>Obrien et al²⁴</p> <p>Aliskiren 150 mg Daily for 3 weeks, if ABPM remained $\geq 135/85$ mm Hg, HCTZ 25 mg Daily was added for an additional 3 weeks</p> <p>vs</p> <p>irbesartan 150 mg Daily for 3 weeks, then aliskiren 75 mg Daily added for 3 weeks, then aliskiren 150 mg Daily added for 3 weeks</p> <p>vs</p> <p>ramipril 5 mg Daily for 3 weeks, then aliskiren 75</p>	<p>3 OL studies</p> <p>Men and women 18 to 80 years of age with ambulatory SBP ≥ 140 and ≤ 180 mm Hg without treatment</p>	<p>N=67</p> <p>6 to 9 weeks</p>	<p>Primary: Change in daytime systolic ABPM with combination therapy compared to monotherapy</p> <p>Secondary: Change in daytime diastolic ABPM, nighttime systolic and diastolic ABPM, daytime and nighttime heart rates, and plasma renin activity</p>	<p>Primary: Aliskiren coadministered with HCTZ (<i>P</i>=0.0007) or ramipril (<i>P</i>=0.03) led to significantly greater reductions in daytime systolic ABPM compared to monotherapy. There was a trend for a reduction in daytime systolic ABPM with the addition of aliskiren to irbesartan; however, this trend was not statistically significant (<i>P</i> value not reported).</p> <p>Secondary: Aliskiren plus HCTZ significantly lowered daytime diastolic ABPM compared to aliskiren monotherapy (<i>P</i>=0.0006). Changes in nighttime systolic and diastolic ABPM followed similar trends but did not achieve statistical significance (<i>P</i>=0.06 and <i>P</i>=0.09, respectively). No changes in heart rate were observed with either aliskiren regimen.</p> <p>Aliskiren added to irbesartan did not significantly change diastolic ABPM compared to irbesartan monotherapy; however, nighttime systolic and diastolic ABPM were significantly reduced (all <i>P</i><0.05). No changes in heart rate were observed with either irbesartan regimen.</p> <p>Mean diastolic ABPM was significantly decreased with the addition of aliskiren 150 mg (<i>P</i><0.05) but not aliskiren 75 mg (<i>P</i> value not reported) to ramipril monotherapy. Both aliskiren doses significantly decreased nighttime systolic and</p>

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<p>mg Daily added for 3 weeks, then aliskiren 150 mg Daily added for 3 weeks</p>				<p>diastolic ABPM (all $P<0.05$). No changes in heart rate were observed with either ramipril regimen.</p> <p>Aliskiren alone significantly inhibited plasma renin activity by 65% ($P<0.0001$), while ramipril and irbesartan monotherapy increased renin activity by 90 and 175%, respectively. When aliskiren was coadministered with HCTZ, ramipril or irbesartan, plasma renin activity remained similar to baseline levels or decreased.</p>
<p>Oparil et al²⁵</p> <p>Aliskiren 150 mg Daily for 4 weeks followed by 300 mg Daily for 4 weeks</p> <p>vs</p> <p>valsartan 160 mg Daily for 4 weeks followed by 320 mg Daily for 4 weeks</p> <p>vs</p> <p>aliskiren/valsartan 150/160 mg Daily for 4 weeks followed by 300/320 mg Daily for 4 weeks</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, PG, RCT</p> <p>Men and women ≥ 18 years of age with stage 1 to 2 essential hypertension (mean sitting DBP 95 to 109 mm Hg and 8-hour ambulatory DBP ≥ 90 mm Hg)</p>	<p>N=1,797</p> <p>8 weeks (4 weeks with forced titration to double the dose to the maximum recommended dose for another 4 weeks)</p>	<p>Primary: Change in mean sitting DBP</p> <p>Secondary: Change in mean sitting SBP, proportion of patients achieving a successful response to treatment (mean sitting DBP <90 mm Hg and/or ≥ 10 mm Hg reduction from baseline) or achieving BP control (mean sitting SBP/DBP $<140/90$ mm Hg), change in 24-hour ABPM, change in biomarkers, and safety</p>	<p>Primary: At week eight, the combination of aliskiren 300 mg plus valsartan 320 mg lowered mean sitting DBP from baseline by 12.2 mm Hg, significantly more than either monotherapy with aliskiren 300 mg (-9.0 mm Hg; $P<0.0001$), valsartan 320 mg (-9.7 mm Hg; $P<0.0001$) or with placebo (-4.1 mm Hg; $P<0.0001$). Monotherapy with aliskiren or valsartan provided significantly greater reductions in mean sitting DBP than did placebo at week eight ($P<0.0001$).</p> <p>Secondary: At week eight, the combination of aliskiren 300 mg plus valsartan 320 mg lowered mean sitting SBP from baseline by 17.2 mm Hg, significantly more than either monotherapy with aliskiren 300 mg (-13.0 mm Hg; $P<0.0001$), valsartan 320 mg (-12.8 mm Hg; $P<0.0001$) or with placebo (-4.6 mm Hg; $P<0.0001$). Monotherapy with aliskiren or valsartan provided significantly greater reductions in mean sitting SBP than did placebo at week eight end point ($P<0.0001$).</p> <p>The proportion of patients achieving a successful response to treatment at week eight was significantly higher with the combination of aliskiren and valsartan (66%) than with aliskiren alone (53%; $P=0.0003$) or valsartan alone (55%; $P=0.0010$). All active treatments were associated with significantly greater responder rates than placebo (30%; $P<0.0001$).</p> <p>The proportion of patients achieving BP control was significantly greater in the combination group (49%) than in the aliskiren (37%; $P=0.0005$) or valsartan (34%; $P<0.0001$) monotherapy groups. All active treatments were associated with significantly greater control rates than placebo (16%; all $P<0.0001$).</p> <p>The combination of aliskiren and valsartan was significantly more effective in lowering mean 24-hour ambulatory SBP and DBP than was either agent alone (all</p>

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				<p>$P < 0.0001$). The greater reductions in ambulatory BP with aliskiren plus valsartan were maintained throughout the entire 24-hour dosing interval.</p> <p>Aliskiren plus valsartan ($P < 0.0001$) and monotherapy with aliskiren ($P < 0.0001$) or valsartan ($P = 0.0002$) provided significant increases in plasma renin concentrations versus placebo. Increases in plasma renin concentrations were significantly greater for the combination than aliskiren ($P = 0.0014$) or valsartan ($P < 0.0001$) monotherapy.</p> <p>Valsartan monotherapy produced significantly greater increases in plasma renin activity than placebo (160 vs 18%; $P = 0.0003$). By contrast, aliskiren alone significantly reduced plasma renin activity by 73% ($P < 0.0001$ vs placebo), while the combination of aliskiren plus valsartan led to a reduction in plasma renin activity of 44% ($P < 0.0001$ vs placebo).</p> <p>The combination of aliskiren and valsartan (-31%; $P < 0.0001$) and valsartan monotherapy (-25%; $P = 0.0007$) provided significantly greater reductions in plasma aldosterone concentration than did placebo ($+7\%$), while aliskiren monotherapy had no significant effect (-5.9%; $P = 0.1059$).</p> <p>Rates of adverse events and laboratory abnormalities were similar in all groups.</p>
<p>Yarows et al²⁶</p> <p>Aliskiren 150 mg Daily for 4 weeks followed by 300 mg Daily for 4 weeks</p> <p>vs</p> <p>valsartan 160 mg Daily for 4 weeks followed by 320 mg Daily for 4 weeks</p> <p>vs</p>	<p>PG, RCT</p> <p>Men and women ≥ 18 years of age with stage 1 to 2 essential hypertension (mean sitting DBP 95 to 109 mm Hg and 8-hour ambulatory DBP ≥ 90 mm Hg)</p>	<p>N=1,797</p> <p>8 weeks</p>	<p>Primary: Change in mean sitting DBP</p> <p>Secondary: Change in mean sitting SBP, proportion of patients achieving a successful response to treatment (mean sitting DBP < 90 mm Hg and/or ≥ 10 mm Hg reduction)</p>	<p>Primary: In patients with stage 2 hypertension, significantly greater reductions in DBP were demonstrated in the aliskiren/valsartan 300/320 mg group compared to either higher-dose monotherapy group ($P < 0.05$) and placebo ($P < 0.0001$).</p> <p>Secondary: In patients with stage 2 hypertension, significantly greater reductions in SBP were demonstrated in the aliskiren/valsartan 300/320 mg group compared to either higher-dose monotherapy group ($P < 0.05$) and placebo ($P < 0.0001$).</p> <p>DBP and SBP reductions in both monotherapy groups were significantly greater compared to placebo ($P < 0.0001$).</p> <p>The proportion of patients with stage 2 hypertension achieving BP control at week eight was significantly greater in the aliskiren/valsartan 300/320 mg group</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>aliskiren/valsartan 150/160 mg Daily for 4 weeks followed by 300/320 mg Daily for 4 weeks</p> <p>vs</p> <p>placebo</p> <p>This is a post-hoc analysis from Oparil et al²⁵ of patients with stage 2 hypertension.</p>			<p>from baseline) or achieving BP control (mean sitting SBP/DBP <140/90 mm Hg)</p>	<p>compared to both monotherapy groups and placebo ($P \leq 0.044$).</p> <p>BP control rates in the aliskiren group were significantly greater than placebo ($P < 0.001$). No significant difference was observed between the valsartan monotherapy and placebo groups.</p>
<p>Pool et al²⁷</p> <p>Aliskiren 75, 150 or 300 mg Daily</p> <p>vs</p> <p>valsartan 80, 160 or 320 mg</p> <p>vs</p> <p>aliskiren/valsartan 75, 150 or 300/80, 160 or 320 mg, respectively</p> <p>vs</p> <p>valsartan/HCTZ 160/12.5 mg</p>	<p>DB, MC, PC, PG, RCT</p> <p>Men and women 18 years of age and older with mild-to-moderate essential hypertension (mean sitting DBP ≥ 95 mm Hg after a 3- to 4-week single-blind placebo run-in period)</p>	<p>N=1,123</p> <p>8 weeks</p>	<p>Primary: Change in mean sitting DBP</p> <p>Secondary: Change in mean sitting SBP, efficacy of aliskiren and valsartan combinations compared to the respective monotherapies and valsartan plus hydrochlorothiazide combination therapy, and safety</p>	<p>Primary: Aliskiren 300 mg significantly ($P < 0.0001$) lowered mean sitting DBP compared to placebo. Reductions in mean sitting DBP for aliskiren 75 and 150 mg compared to placebo failed to reach statistical significance ($P = 0.052$ and $P = 0.051$, respectively).</p> <p>Secondary: Aliskiren 300 mg significantly ($P < 0.0001$) lowered mean sitting SBP compared to placebo.</p> <p>A statistically significant linear dose relationship was observed for the effect of aliskiren (75 to 300 mg) on mean sitting DBP ($P = 0.0002$) and mean sitting SBP ($P = 0.0005$). The effects of aliskiren monotherapy on mean sitting DBP and SBP across the 75 to 300 mg dose range were similar to the effects of valsartan 80 to 320 mg.</p> <p>Coadministration of aliskiren and valsartan produced a greater antihypertensive effect than either drug alone. Reductions in mean sitting DBP and SBP obtained with aliskiren/valsartan 150/160 mg and aliskiren/valsartan 300/320 mg were not significantly different from those observed with valsartan/HCTZ 160/12.5 mg.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo				<p>Responder rates were significantly greater than placebo for all three aliskiren monotherapy groups and for all aliskiren/valsartan combinations. The proportion of responders with aliskiren/valsartan 75/80 mg was significantly greater than either component monotherapy ($P<0.05$). There was no significant difference between the proportion of responders to aliskiren/valsartan 150/160 mg or aliskiren/valsartan 300/320 mg compared to valsartan/HCTZ 160/12.5 mg.</p> <p>Control rates were higher with aliskiren 300 mg compared to placebo and with valsartan/HCTZ 160/12.5 mg compared to aliskiren/valsartan 150/160 mg, but there were no significant differences between aliskiren/valsartan combinations and the respective monotherapies.</p> <p>Aliskiren and valsartan were generally well tolerated either as monotherapy or in combination. The overall incidence of adverse events and rate of discontinuations because of adverse events were similar to placebo in all active treatment groups.</p>

Drug regimen abbreviations: HCTZ=hydrochlorothiazide

Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, DD=double-dummy, MA=meta-analysis, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, RR=relative risk, XO=cross-over

Miscellaneous abbreviations: ABPM=ambulatory blood pressure monitoring, BMI=body mass index, BP=blood pressure, DBP=diastolic blood pressure, mm Hg=millimeters of mercury, SBP=systolic blood pressure

Special Populations**Table 5. Special Populations^{1,8-11}**

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Single Entity Agents					
Aliskiren	No dosage adjustment required in the elderly population. Safety and efficacy have not been established in pediatric patients under the age of 18.	No dosage adjustment required.	No dosage adjustment required.	C (first trimester) D (second and third trimester)	Unknown
Combination Products					
Aliskiren/ amlodipine	No dosage adjustment required in the elderly population. Safety and efficacy have not been established in pediatric patients under the age of 18.	Not studied in patients with renal dysfunction.	Not studied in patients with hepatic dysfunction. Amlodipine is extensively metabolized by the liver and its plasma elimination half-life is prolonged in patients with hepatic impairment. Caution should be exercised in this population. The starting dose of amlodipine in this population is 2.5 mg.	D	Unknown
Aliskiren/ amlodipine/ hydrochloro- thiazide	No dosage adjustment required in the elderly population. Safety and efficacy have not been established in pediatric patients under the age of 18.	Loop diuretics are preferred to thiazides in patients with severe renal impairment. Up titrate hydrochloro-thiazide slowly.	Amlodipine is extensively metabolized by the liver and its plasma elimination half-life is prolonged in patients with hepatic impairment. The starting dose of amlodipine in	D	Unknown

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
			this population is 2.5 mg, a dose not available in Amturnide. Caution should be exercised in this population.		
Aliskiren/ hydrochloro- thiazide	No dosage adjustment required in the elderly population. Safety and efficacy have not been established in pediatric patients under the age of 18.	Loop diuretics are preferred to thiazides in patients with severe renal impairment. Up titrate hydrochloro-thiazide slowly.	Uptitrate slowly; minor alterations in fluid and electrolyte balance may precipitate hepatic coma.	D	Unknown
Aliskiren/ valsartan	No dosage adjustment required in the elderly population. Safety and efficacy have not been established in pediatric patients under the age of 18.	Not studied in patients with renal dysfunction.	Patients with mild to moderate hepatic impairment showed lower valsartan clearance.	D	Unknown

Adverse Drug Events

Adverse effects presented in Table 6 are those reported in the prescribing information for the combination products. These adverse effects may differ from those reported for each individual agent, which are covered in their respective single entity product reviews.

Table 6. Adverse Drug Events (%)^{1,8-11}

Adverse Event(s)	Single Entity Agents	Combination Products			
	Aliskiren	Aliskiren/ amlodipine	Aliskiren/ amlodipine/ hydrochloro- thiazide	Aliskiren/ hydro- chloro- thiazide	Aliskiren/ valsartan
Cardiovascular					
Hypertension, uncontrolled	-	-	-	-	1.4
Central and Peripheral Nervous System					
Asthenia	-	-	-	1.2	-
Dizziness	-	-	3.6	2.3	-
Headache	-	-	3.6	-	-
Vertigo	-	-	-	1.2	1.1

Adverse Event(s)	Single Entity Agents	Combination Products			
	Aliskiren	Aliskiren/ amlodipine	Aliskiren/ amlodipine/ hydrochlorothiazide	Aliskiren/ hydrochlorothiazide	Aliskiren/ valsartan
Dermatologic					
Rash	1	-	-	-	-
Gastrointestinal/Hepatic					
Abdominal pain	✓	-	-	-	-
Diarrhea	2.3	-	-	1.6	1.4
Dyspepsia	✓	-	-	-	-
Gastroesophageal reflux	✓	-	-	-	-
Genitourinary					
Urinary tract infection	-	-	-	-	1.4
Hypersensitivity					
Angioedema	<1	-	-	-	-
Metabolic					
Gout	0.2	-	-	-	-
Hyperkalemia	-	-	-	-	✓
Uric acid elevation	0.4	-	-	-	-
Musculoskeletal					
Arthralgia	-	-	-	1	-
Renal					
Renal stones	0.2	-	-	-	-
Respiratory					
Cough	1.1	-	-	1.3	-
Nasopharyngitis	-	-	2.6	-	2.6
Upper respiratory tract infection	-	-	-	-	1.4
Other					
Edema (face, hands or whole body)	✓	-	-	-	-
Fatigue	-	-	-	-	2.6
Influenza	-	-	-	2.3	1.1
Periorbital edema	✓	-	-	-	-
Peripheral edema	✓	6.2 to 8.9	7.1	-	-

✓ Percent not specified.

-Event not reported.

Contraindications/Precautions

Aliskiren

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. This has resulted in the black box warning outlined below. If this drug is used during pregnancy or if a woman becomes pregnant while on this drug, she should be apprised of the potential fetal risk.^{1,8-11}

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx requiring hospitalization and intubation has been reported with aliskiren. Airway obstruction may occur and may be fatal. Angioedema may occur at any time during treatment. Prompt administration of subcutaneous epinephrine solution and measures to preserve airway patency may be necessary. Aliskiren should be discontinued and not readministered in patients experiencing this effect.^{1,8-11}

Symptomatic hypotension may occur after initiation of aliskiren in patients with an activated renin-angiotensin system, such as those who are volume- and/or salt-depleted. This condition should be corrected before administration of aliskiren. If an excessive fall in blood pressure occurs, the patients should be placed in the supine position and given an intravenous infusion of normal saline if necessary. A transient hypotensive response does not contraindicate further treatment once blood pressure has been stabilized.^{1,8-11}

Routine monitoring of electrolytes and renal function is indicated in diabetic patients taking aliskiren and angiotensin converting enzyme (ACE) inhibitors concurrently. Increases in serum potassium were more frequent in this population compared to monotherapy with aliskiren in patients without diabetes.¹

Concomitant use of aliskiren with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other drugs that increase potassium may lead to increases in serum potassium levels. Caution should be exercised in this patient population.¹

Periodic monitoring of serum electrolyte is indicated in patients with severe renal impairment.¹

Concurrent use of aliskiren and cyclosporine or itraconazole results in a significant increase in blood concentrations of aliskiren. Concurrent use is not recommended.^{1,8-11}

Amlodipine

Amlodipine is extensively metabolized by the liver and the plasma elimination half-life is 56 hours in patients with impaired hepatic function. Caution is recommended when administering Tekamlo[®] to patients with severe hepatic impairment.⁸

Hydrochlorothiazide

Loop diuretics are preferred over thiazide diuretics in patients with severe renal impairment.^{9,10}

Uptitrate slowly in patients with hepatic impairment. Minor alterations in fluid and electrolyte balance may precipitate hepatic coma.^{9,10}

Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma but are more likely in patients with such a history.^{9,10}

Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.^{9,10}

Lithium should generally not be given with thiazide diuretics.^{9,10}

Hydrochlorothiazide can cause an idiosyncratic reaction resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. Hydrochlorothiazide should be discontinued immediately. Prompt medical or surgical treatments may be needed.^{9,10}

Tekamlo[®]

Rarely, initiation or change to the dose of a calcium channel blocker may result in the development of documented increased frequency, duration and severity of angina or acute myocardial infarction particularly in patients with severe obstructive coronary artery disease.⁸

Tekturna HCT[®]

Periodic determinations of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.¹⁰

Valsartan

No data are available on the use of valsartan in patients with unilateral or bilateral renal artery stenosis. An effect similar to that seen with ACE inhibitors should be anticipated (i.e. increase in serum creatinine or blood urea nitrogen).¹¹

In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors and angiotensin receptor antagonists has been associated with oliguria or progressive azotemia and (rarely) with acute renal failure or death. Similar outcomes have been reported with valsartan.¹¹

Patients with hepatic impairment showed lower valsartan clearance.¹¹

Some patients with heart failure have developed increases in blood urea nitrogen, serum creatinine and potassium on valsartan. The effects are typically mild and transient and are more likely to occur in patients with renal impairment. Dosage reduction and/or discontinuation may be required. Include assessment of renal function in patients with heart failure or post-myocardial infarction.¹¹

Valturna[®]

Periodic determinations of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. Caution is advised with concurrent use of Valturna[®] and potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other drugs that increase potassium levels.¹¹

Black Box Warning^{1,8-11}

WARNING
When pregnancy is detected, discontinue Amturnide [®] /Tekamlo [®] /Tekturna [®] /Tekturna HCT [®] /Valturna [®] as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. [See Warnings and Precautions.]

Drug Interactions

Table 7. Drug Interactions^{1,8-11,15}

Generic Name	Interacting Medication or Disease	Mechanism
Aliskiren	Angiotensin-converting enzyme inhibitors	Aliskiren has been associated with infrequent increases in serum potassium of >5.5 meq/L (0.9 vs 0.6% with placebo). When aliskiren was used in combination with an ACE inhibitor in a diabetic population, increases in serum potassium were more frequent (5.5%). Use caution when aliskiren is given concurrently with angiotensin-converting enzyme inhibitors. Routine monitoring of electrolytes and renal function is indicated in this population.
Aliskiren	Cyclosporine	Concurrent administration of aliskiren 75 mg with 200 and 600 mg of cyclosporine led to an approximate 2.5-fold increase in aliskiren maximum concentration and 5-fold increase in aliskiren area under the curve. Concurrent use is not recommended.
Aliskiren	Furosemide	Concurrent administration of aliskiren with furosemide resulted in decreases of 30 and 50% in furosemide area under the curve and maximum concentration, respectively. Caution is advised if these agents are used concurrently.
Aliskiren	Itraconazole	Itraconazole increases the absorption of aliskiren by inhibition of P-glycoprotein. Itraconazole may also decrease the metabolism of aliskiren by inhibition of CYP 3A4. Concurrent use is not recommended.

Generic Name	Interacting Medication or Disease	Mechanism
Aliskiren	Ketoconazole	Concurrent administration with ketoconazole (CYP3A4 inhibitor) led to an increase in plasma levels of aliskiren. Caution is advised if administered concurrently with ketoconazole.
Aliskiren	Potassium-sparing diuretics	Concurrent administration may result in hyperkalemia. Monitoring electrolytes and renal function is recommended.
Aliskiren	Potassium supplements	Concurrent administration may result in hyperkalemia. Monitoring of electrolytes and renal function is recommended.
Hydrochlorothiazide	Cisapride	Cisapride is contraindicated in patients receiving thiazide diuretics. Thiazide diuretics may lead to a rapid reduction in plasma potassium. This electrolyte loss may lead to additive prolongation of the QT interval, increasing the risk of life-threatening arrhythmias.
Hydrochlorothiazide	Diazoxide	Hyperglycemia and symptoms similar to frank diabetes may occur. The effect appears to return to pre-treatment values approximately two weeks after discontinuation of the medications. Decreased dose of one or both medications may be indicated. Avoidance of concurrent use is recommended with close monitoring of blood and urine glucose levels if concurrent use is necessary.
Hydrochlorothiazide	Digitalis glycosides	Thiazide diuretics may induce electrolyte disturbances which may predispose patients to digitalis-induced arrhythmias. Measure plasma levels of potassium and magnesium, supplement low levels, and use dietary sodium restriction or potassium-sparing diuretics to prevent further losses.
Hydrochlorothiazide	Dofetilide	Thiazide diuretics may induce hypokalemia which may increase the risk of torsades de pointes. The coadministration of dofetilide with a thiazide diuretic is contraindicated.
Hydrochlorothiazide	Lithium	Decreased lithium clearance may occur with thiazide use. This may lead to increased serum lithium levels and possibly lithium toxicity. Monitor plasma lithium levels and symptoms of toxicity, and adjust the dose as needed.
Hydrochlorothiazide	Loop diuretics (bumetanide, ethacrynic acid, furosemide, torsemide)	Coadministration may lead to greater sodium, potassium and chloride excretion and diuresis. Careful titration with small or intermittent doses is recommended. Monitor for dehydration and electrolyte abnormalities during concurrent use.
Hydrochlorothiazide	Sulfonylureas	Thiazide diuretics may decrease insulin tissue sensitivity, decrease insulin secretion, and increase potassium loss. This may lead to hyperglycemia, decreasing the hypoglycemic effects of the sulfonylureas. Blood glucose levels should be closely monitored, and an increase of the sulfonylurea dose may be needed.
Valsartan	Lithium	Concurrent use may result in elevated lithium levels and possibly lithium toxicity. Monitor for lithium toxicity and adjust lithium dose as needed.
Valsartan	Potassium-sparing diuretics	Concurrent use may result in elevated serum potassium concentrations in high-risk patients (renal impairment, type 2 diabetes). Monitoring of serum potassium and renal function is recommended. Consider estimating creatinine clearance in elderly and high-risk patients.

Dosage and Administration**Table 8. Dosing and Administration**^{1,8-11}

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Aliskiren	<u>Treatment of hypertension either alone or in combination with other antihypertensive agents:</u> Initial, 150 mg Daily; may increase daily dose to 300 mg if blood pressure not adequately controlled	Safety and efficacy have not been established in pediatric patients under the age of 18.	Tablet: 150 mg 300 mg
Combination Products			
Aliskiren/ amlodipine	<u>Treatment of hypertension as initial therapy in patients likely to need multiple drugs to achieve blood pressure goals, treatment of hypertension in patients not adequately controlled with monotherapy, treatment of hypertension as a substitute for its titrated components:</u> Initial, 150/5 mg Daily; maximum, 300/10 mg	Safety and efficacy have not been established in pediatric patients under the age of 18.	Tablet: 150/5 mg 150/10 mg 300/5 mg 300/10 mg
Aliskiren/ amlodipine/ hydrochloro- thiazide	<u>Treatment of hypertension; not as initial therapy</u> Dose Daily; maximum, 300/10/25 mg Daily	Safety and efficacy have not been established in pediatric patients under the age of 18.	Tablet: 150/5/12.5 mg 300/5/12.5 mg 300/5/25 mg 300/10/12.5 mg 300/10/25 mg
Aliskiren/ hydrochloro- thiazide	<u>Treatment of hypertension as initial therapy in patients likely to need multiple drugs to achieve blood pressure goals, treatment of hypertension in patients not adequately controlled with monotherapy:</u> Initial, 150/12.5 mg Daily; maximum, 300 mg/25 mg Daily	Safety and efficacy have not been established in pediatric patients under the age of 18.	Tablet: 150/12.5 mg 150/25 mg 300/12.5 mg 300/25 mg
Aliskiren/ valsartan	<u>Treatment of hypertension as initial therapy in patients likely to need multiple drugs to achieve blood pressure goals, treatment of hypertension in patients not adequately controlled with monotherapy, treatment of hypertension as a substitute for its titrated components:</u> Initial, 150/160 mg Daily; maximum, 300/320 mg	Safety and efficacy have not been established in pediatric patients under the age of 18.	Tablet: 150/160 mg 300/320 mg

Clinical Guidelines**Table 9. Clinical Guidelines**

Clinical Guideline	Recommendations
National Heart, Lung, and Blood Institute: The Seventh Report of The Joint National Committee on Prevention, Detection,	<ul style="list-style-type: none"> Thiazide-type diuretics should be used as initial therapy for most patients with hypertension, either alone or in combination with another class (angiotensin converting enzyme [ACE] inhibitors, angiotensin II receptor blockers [ARBs], β-blockers, calcium channel blockers) demonstrated to be beneficial in randomized controlled outcome trials

Clinical Guideline	Recommendations
<p>Evaluation, and Treatment of High Blood Pressure (JNC 7) (2004)³⁸</p>	<ul style="list-style-type: none"> • Certain high-risk conditions are compelling reasons for initiating therapy with a drug from another class including β-blockers, ACE inhibitors, ARBs or calcium channel blockers. This recommendation is based on the results of several large trials, including the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial that showed diuretics to be more effective than other antihypertensive agents in preventing cardiovascular complications. • Most patients will need more than one antihypertensive medication to achieve blood pressure goals. Most patients with stage 2 hypertension will require initial therapy with medications from two drug classes. • When a single drug in adequate doses fails to achieve the blood pressure goal, then a second agent from a different class should be added to the treatment regimen. Initial treatment with two antihypertensive agents should be considered for patients with a baseline blood pressure of more than 20/10 mm Hg above goal. However, caution should be used with patients who are at increased risk of orthostatic hypotension. One of the agents should be a thiazide diuretic. • High-risk conditions with compelling indications for individual drug classes are as follows: heart failure (diuretics, ACE inhibitors, β-blockers, ARBs and aldosterone antagonists), post-myocardial infarction (β-blockers, ACE inhibitors and aldosterone antagonists), high coronary disease risk (diuretics, ACE inhibitors, β-blockers and calcium channel blockers), diabetes (diuretics, ACE inhibitors, ARBs, β-blockers and calcium channel blockers), chronic kidney disease (ACE inhibitors and ARBs) and recurrent stroke prevention (diuretics and ACE inhibitors). • The drug of choice in patients with hypertension and stable angina is a β-blocker. Long-acting calcium channel blockers may also be used. • For asymptomatic patients with ventricular dysfunction, ACE inhibitors and β-blockers are recommended. For patients with symptomatic ventricular dysfunction or end-stage heart disease, ACE inhibitors, ARBs, β-blockers and aldosterone antagonists are recommended. • Thiazide diuretics, ACE inhibitors, ARBs, β-blockers and calcium channel blockers are beneficial in reducing cardiovascular disease and stroke in patients with diabetes. ACE inhibitors and ARBs have been shown to favorably affect the progression of diabetic nephropathy and reduce albuminuria, and ARBs have been shown to reduce the progression to microalbuminuria. • Patients with chronic kidney disease often require treatment with three or more antihypertensive agents to achieve a blood pressure goal of <130/80 mm Hg. ACE inhibitors and ARBs have been shown to be beneficial in patients with diabetic and nondiabetic kidney disease. As renal disease advances, increasing doses of loop diuretics are often required, along with other medications. • African American patients have shown decreased responses to monotherapy with ACE inhibitors, ARBs and β-blockers compared to calcium channel blockers and diuretics. The incidence of ACE-inhibitor-induced angioedema is two to four times higher in African Americans. • Calcium channel blockers may be useful in Raynaud's syndrome and certain arrhythmias. • ACE inhibitors and ARBs should not be given to women who are pregnant or may become pregnant.

Clinical Guideline	Recommendations
<p>World Health Organization/ International Society of Hypertension: 2003 World Health Organization/ International Society of Hypertension Statement on Management of Hypertension (2003)³⁹</p>	<ul style="list-style-type: none"> • When used as monotherapy, a diuretic or a calcium channel blocker may be more effective than an ACE inhibitor or a β-blocker in African American patients and older patients. • Compelling indications for the use of a medication from a specific drug class include elderly patients with isolated systolic hypertension (diuretics and dihydropyridine calcium channel blockers), renal disease (ACE inhibitors and ARBs), post-myocardial infarction (ACE inhibitors and β-blockers), left ventricular dysfunction (ACE inhibitors), congestive heart failure (β-blockers, ACE inhibitors and diuretics), left ventricular hypertrophy (ARBs) and cerebrovascular disease (diuretics and ACE inhibitors).
<p>European Society of Hypertension/ European Society of Cardiology: 2007 Guidelines for the Management of Hypertension (2007)⁴⁰, Reappraisal of Guidelines on Hypertension Management (2009)⁷</p>	<ul style="list-style-type: none"> • In order to optimize treatment initiation, intensity and goals, it is important to assess total cardiovascular risk in patients with hypertension which must include a search for subclinical organ damage. • In general, early introduction of blood pressure lowering treatments, before organ damage develops or becomes irreversible or before cardiovascular events occur, is recommended. • There is evidence that certain drug classes may be preferred in specific patient populations: left ventricular hypertrophy (ACE inhibitors, ARBs and calcium channel blockers), asymptomatic atherosclerosis (calcium channel blockers and ACE inhibitors), microalbuminuria and renal dysfunction (ACE inhibitors and ARBs), previous stroke (any antihypertensive), previous myocardial infarction (ACE inhibitors, β-blockers and ARBs), angina (calcium channel blockers and β-blockers), heart failure (diuretics, ACE inhibitors, β-blockers, ARBs and aldosterone antagonists), recurrent atrial fibrillation (ACE inhibitors and ARBs), permanent atrial fibrillation (β-blockers and nondihydropyridine calcium channel blockers), end stage renal disease/proteinuria (ACE inhibitors, ARBs and loop diuretics), metabolic syndrome (ACE inhibitors, ARBs and calcium channel blockers), diabetes (ACE inhibitors and ARBs), pregnancy (methyldopa, calcium channel blockers and β-blockers) and African American patients (calcium channel blockers and diuretics). • Available evidence justifies the use of aliskiren in hypertension, particularly in combination with other agents. • Many patients will require more than one medication to control blood pressure. Patients may be started on monotherapy or combination therapy. Initial combination therapy should be considered in patients with grade II or III hypertension or patients with high or very high cardiovascular risk. • Fixed combination medications can favor compliance and simplify regimens. • When combining different classes of antihypertensive medications, consider medications which have different and complementary mechanisms of action, and that there is evidence that the antihypertensive effect of the combination is greater than that of either combination component and the combination is likely to be well tolerated. <ul style="list-style-type: none"> • Combinations that can be recommended for priority use based on trial evidence of outcome reduction include a diuretic with an ACE inhibitor, ARB or calcium channel blocker and an ACE inhibitor with a calcium channel blocker.

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> • Avoid β-blocker/diuretic combination unless required for other reasons. • If triple therapy is needed, the most rational combination is a blocker of the rennin-angiotensin system, a calcium channel blocker and a diuretic at effective doses. • A β- or α-blocker may be included in a triple therapy approach depending on clinical circumstances. • Antihypertensive treatment is highly beneficial in elderly patients and treatment may be initiated with a thiazide diuretic, ACE inhibitor, calcium channel blocker, ARB or β-blocker. • Blood pressure lowering drugs should be continued or initiated in patients 80 years of age, starting with monotherapy and adding a second drug, if needed. The decision to treat should be made on an individual basis and patients should be carefully monitored. • Calcium channel blockers, ARBs and thiazide diuretics have been shown to be effective in treating isolated systolic hypertension. • Antihypertensive treatment should always be initiated in diabetic patients when blood pressure is 140/90 mm Hg or higher; however, there is evidence in favor of initiating treatment with high normal blood pressure. • The blood pressure goal of <130/80 mm Hg is not supported by outcome evidence from trials and is difficult for the majority of patients to achieve; therefore, its realistic to recommend only to pursue a sizeable blood pressure reduction without indicating a goal that is unproven. • In hypertensive diabetic patients, tight blood glucose control (glycosylated hemoglobin to 6.5%) is beneficial, particularly in combination with effective blood pressure control, on improving microvascular complications. Tight glucose control should not be pursued abruptly and patients should be monitored closely due to the increased risk of severe hypoglycemic episodes.
<p>National Institute for Health and Clinical Excellence/British Hypertension Society: Hypertension: Management in Adults in Primary Care: Pharmacological Update (2006)⁴⁰¹</p>	<ul style="list-style-type: none"> • Initial therapy in patients ≥ 55 years of age should be a calcium channel blocker or a thiazide diuretic. • Initial therapy in patients <55 years of age should be an ACE inhibitor or an ARB if the patient is intolerant to ACE inhibitors. • If a second medication is required and initial therapy was with a calcium channel blocker or diuretic, an ACE inhibitor should be added. If initial therapy was with an ACE inhibitor, a calcium channel blocker or a diuretic should be added. • If three medications are required, a combination of calcium channel blocker, ACE inhibitor and diuretic should be used. If blood pressure remains uncontrolled, consider adding a fourth medication or consult a specialist.

Conclusions

Aliskiren is the only single entity renin inhibitor marketed in the United States and it is not available generically. Aliskiren is Food and Drug Administration (FDA) approved for the treatment of hypertension, either alone or in combination with other antihypertensive agents.¹ Clinical trials have demonstrated that aliskiren 150 to 300 mg once daily is significantly more effective than placebo in lowering both systolic and diastolic blood pressures in men and women with mild-to-moderate essential hypertension.^{17,29} Doses above 300 mg did not result in an increased blood pressure response but increased the rate of diarrhea.²⁹ Aliskiren was associated with an increase in plasma renin concentrations but a decrease in plasma renin activity.²⁹

Limited comparative trials of aliskiren with other antihypertensive agents, including the angiotensin-converting enzyme inhibitors¹⁶ and angiotensin receptor blockers¹⁷⁻¹⁹ have generally demonstrated similar efficacy when administered in comparable doses. In general, the incidence of side effects was also comparable. One study reported better efficacy with aliskiren compared to ramipril, and a higher incidence of cough with ramipril (5.5 vs 2.1%).²⁰ Schmieder et al compared monotherapy with aliskiren to monotherapy with hydrochlorothiazide and demonstrated significantly lower systolic and diastolic blood pressures at weeks six and 12 with aliskiren in addition to better overall response rates, though the significant difference in systolic blood pressure was not maintained at week 52.²¹ When administered to hypertensive patients with diabetic nephropathy who were already receiving losartan, aliskiren reduced the mean urinary albumin:creatinine ratio by 20% compared to placebo with only small differences in blood pressure.³⁵ Additional studies are needed to determine the role of aliskiren in hypertensive patients with diabetic nephropathy.

Overall, aliskiren appears to be well tolerated with clinical trials reporting adverse events similar to placebo at doses up to 300 mg daily.⁵ Like other drugs that act directly on the renin-angiotensin-aldosterone system, aliskiren carries a black box warning against use during pregnancy.¹

The combination renin inhibitors are also FDA approved for the treatment of hypertension.⁸⁻¹¹ There are four combination renin inhibitors available currently, and none are available generically. One product, Amturnide[®], is a combination of three antihypertensive medications- aliskiren, amlodipine and hydrochlorothiazide- and is not indicated for initial treatment of hypertension.⁹

Clinical trials have evaluated the use of aliskiren in combination with amlodipine, hydrochlorothiazide and valsartan in the treatment of hypertension. In general, the combination groups showed significantly greater blood pressure-lowering efficacy compared to monotherapy with each individual agent or placebo.²²⁻²⁷ Drummond et al compared the combination of daily aliskiren/amlodipine 150/5 mg to monotherapy with amlodipine 5 or 10 mg daily in patients not fully responding to monotherapy with amlodipine 5 mg daily. Significant reductions in systolic and diastolic blood pressure were observed when comparing combination therapy to amlodipine 5 mg, though no significant difference was observed between combination therapy and amlodipine 10 mg. Similar results were observed in the proportion of patients responding to treatment and the proportion of patients achieving blood pressure control.²⁸

To date, there are no long-term trials evaluating the safety and efficacy of aliskiren or determining whether aliskiren improves clinical outcomes. In addition, the role of renin inhibitors has not been addressed by the majority of consensus guidelines for the management of hypertension.^{38,39,41} The European Society of Hypertension/European Society of Cardiology 2009 Reappraisal of Guidelines on Hypertension Management concludes that the use of aliskiren in the treatment of hypertension is justified based on available evidence, particularly when used in combination with other agents.⁷ The completion of ongoing trials with hard endpoints evaluating the use of aliskiren as monotherapy and in combination with other agents will further define the role of aliskiren in the treatment of hypertension.

Appendix I: Other Insurance Coverage of Tekamlo[®] and Amturnide[®]

Managed Care Organization	Current Coverage
MassHealth (Massachusetts Medicaid)	PA required (both products)
New Hampshire Medicaid	Non-preferred, PA required (Tekamlo); Not listed (Amturnide)
New York Medicaid	Non-preferred, PA required (both products)
MVP Healthcare	Not covered; Tier 3; PA required (both products)
Cigna Healthcare	Non-preferred; Tier 3
Blue Cross Blue Shield of Vermont	Step therapy (both products)

Appendix II: Current Preferred Drug List (PDL) Alternatives (to Tekamlo[®] and Amturnide[®])

Medication	Cost/Unit*	Dosing Frequency	Cost/30 days*
Tekamlo[®] (aliskiren/amlodipine) 150/5 mg, 150/10 mg, 300/5 mg, 300/10 mg tablet	\$2.98 (150/5/12.5 mg); \$3.76 (300/5 & 300/10 mg)	once daily	\$98.10-\$123.90
Amturnide[®] (aliskiren/amlodipine/hydrochlorothiazide) 150/5/12.5 mg, 300/5/12.5 mg, 300/5/25 mg, 300/10/12.5 mg, 300/10/25 mg tablet	\$2.98 (150/5/12.5 mg); \$3.76 (300/5/12.5 mg, 300/5/25 mg, 300/10/12.5 mg & 300/10/25 mg)	once daily	\$89.40-\$112.80
Tekturna [®] (aliskiren) 150 mg, 300 mg tablet	\$3.28 (150 mg); \$4.14 (300 mg)	once daily	\$98.40-\$124.20
Tekturna HCT [®] (aliskiren/hydrochlorothiazide) 150/12.5 mg, 150/25 mg, 300/12.5 mg, 300/25 mg tablet	\$3.28 (150/12.5mg & 150/25 mg); \$4.14 (300/12.5 mg & 300/25 mg)	once daily	\$98.40-\$124.20

*AWP per SXC as of 8/3/2011

Appendix III: Utilization Within This Drug Class for DVHA: January 1, 2011 to June 30, 2011

Medication	Unique utilizers	# of Rx's	Market Share (%)	Plan Cost \$	Avg \$/Rx
Tekturna [®]	2	3	43.0%	\$612.12	\$204.04
Tekturna HCT [®]	1	2	28.5%	\$635.86	\$317.93
Valturna [®]	1	2	28.5%	426.46	213.23
Class Total:	4	7	100%	\$1,674.44	\$239.21

Recommendations

In recognition of the following factors:

- The single-entity renin inhibitor aliskiren has shown effectiveness in lowering blood pressure compared to placebo.
- The single-entity renin inhibitor aliskiren has generally demonstrated similar efficacy to other antihypertensive agents, including angiotensin converting enzyme inhibitors and angiotensin II receptor blockers, when administered in comparable doses.
- The combination renin inhibitors have generally shown significantly greater blood pressure-lowering efficacy compared to monotherapy with each individual agent or placebo.
- Clinical trials evaluating the effects of renin inhibitors on clinical outcomes have not been conducted.
- The role of the renin inhibitors has only been addressed by the European Society of Hypertension/European Society of Cardiology's 2009 Reappraisal of the Guidelines on Hypertension Management, which concludes that the use is justified based on available evidence, yet does not state the role of these agents relative to other classes of medication.

...it is recommended that:

Tekamlo[®] and Amturnide[®] be added to the Department of Vermont Health Access (DVHA) Preferred Drug List (PDL) as prior authorization required with the following approval criteria:

Tekamlo®, Amturnide®:

- The patient has a diagnosis of hypertension.
- AND**
- The patient has had a documented side effect, allergy, or treatment failure with an Angiotensin Receptor Blocker (ARB). *Note:* Approval of an ARB requires a documented side effect, allergy, or treatment failure with an Angiotensin Converting Enzyme (ACE) inhibitor.
- OR**
- The patient has had a documented treatment failure with Tekturna® alone.
 - In addition, a quantity limit of 1 tablet/day is recommended.

No changes to the currently managed renin inhibitors are proposed (see below).

Tekturna®:

- The patient has a diagnosis of hypertension.
- AND**
- The patient has had a documented side effect, allergy, or treatment failure with an Angiotensin Receptor Blocker (ARB). *Note:* Approval of an ARB requires a documented side effect, allergy, or treatment failure with an Angiotensin Converting Enzyme (ACE) inhibitor.

Tekturna HCT®:

- The patient has a diagnosis of hypertension.
- AND**
- The patient has had a documented side effect, allergy, or treatment failure with an Angiotensin Receptor Blocker (ARB). *Note:* Approval of an ARB requires a documented side effect, allergy, or treatment failure with an Angiotensin Converting Enzyme (ACE) inhibitor.
- OR**
- The patient has had a documented treatment failure with Tekturna® alone.

Valturna®:

- The patient has a diagnosis of hypertension.
- AND**
- The patient has had a documented side effect, allergy, or treatment failure to an angiotensin converting enzyme inhibitor (ACEI), an ACEI combination or any other angiotensin receptor blocker (ARB) or ARB combination.
- OR**
- The patient has had a documented treatment failure with Tekturna® alone.

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