Therapeutic Class Overview
Renin Inhibitors

Therapeutic Class

- **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] There are four combination renin inhibitor products available in the U.S. which combine aliskiren with other blood pressure-lowering medications from different therapeutic classes including thiazide diuretics, calcium channel blockers and angiotensin receptor blockers. The combination products currently available include aliskiren/amlodipine (Tekamlo®), aliskiren/amlodipine/hydrochlorothiazide (Amturnide®), aliskiren/hydrochlorothiazide (Tekturna HCT®) and aliskiren/valsartan (Valturna®). These agents are also FDA-approved for the treatment of hypertension.[1-5] Renin catalyzes the conversion of angiotensinogen to angiotensin I, which is the first and rate-limiting step of the renin-angiotensin-aldosterone system.[6-8] 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.[8] Angiotensin II exerts other detrimental cardiovascular effects including hypertrophy, inflammation, remodeling and thrombosis. As a direct renin inhibitor, aliskiren reduces angiotensin I, angiotensin II and aldosterone levels by binding to renin with high affinity in the plasma.[7,8] Currently, no single-entity or combination renin inhibitor is available generically.

Table 1. Current Medications Available in Therapeutic Class[1-5]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Aliskiren (Tekturna®)	Treatment of hypertension, either alone or in combination with other antihypertensive agents	Tablet: 150 mg 300 mg	-
Aliskiren/ amlodipine (Tekamlo®)	Treatment of hypertension as initial therapy in patients likely to need multiple drugs to achieve blood pressure goals, in patients not adequately controlled with monotherapy and as a substitute for its titrated components	Tablet: 150/5 mg 150/10 mg 300/5 mg 300/10 mg	-
Aliskiren/ amlodipine/ hydrochlorothiazide (Amturnide®)	Treatment of hypertension, not as initial therapy	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/ hydrochlorothiazide (Tekturna HCT®)	Treatment of hypertension as initial therapy in patients likely to need multiple drugs to achieve blood pressure goals, in patients not adequately controlled with monotherapy	Tablet: 150/12.5 mg 150/25 mg 300/12.5 mg 300/25 mg	-
Aliskiren/valsartan (Valturna®)	Treatment of hypertension as initial therapy in patients likely to need multiple drugs to achieve blood pressure goals, in patients not adequately controlled with monotherapy and as a substitute for its titrated components	Tablet: 150/160 mg 300/320 mg	-

Evidence-based Medicine

- Published 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.[10-15]
- 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 combination therapy to amlodipine 5 mg, though no significant difference was observed between 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.[14] In a sub-analysis, similar results were observed in the proportion of patients responding to treatment and the proportion of patients achieving blood pressure control.[16]
- In two studies, the combination of aliskiren/hydrochlorothiazide was shown to be significantly more effective than hydrochlorothiazide and aliskiren monotherapy at reducing systolic blood pressure after 8 and 12 weeks, respectively (P<0.0001 compared to monotherapy in both studies). Similarly, greater improvements in diastolic blood pressure were also achieved with aliskiren/hydrochlorothiazide in both studies compared to treatment with monotherapy (P<0.0001 compared to monotherapy in both studies). [17,18]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - 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.[9] 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 guidelines have addressed the role of aliskiren in the management of patients with hypertension.[19-21]
- Other Key Facts:
    - In the Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints (ALTITUDE) trial, there was an increased incidence of non-fatal stroke, renal complications, hyperkalemia and hypotension in the aliskiren treatment arm when added to standard care in patients with type 2 diabetes mellitus and concomitant renal impairment. Aliskiren-containing products for use in combination with an angiotensin converting enzyme (ACE)-inhibitor or angiotensin II receptor blocker (ARB) will no longer be promoted by the manufacturer.[22]
    - The American Association of Clinical Endocrinologists recommends that physicians transition away from the use of aliskiren in combination with ACE inhibitor or angiotensin II receptor blocker in patients with diabetes and chronic kidney disease.[23]
    - Clinical trials have demonstrated the safety and efficacy of aliskiren as monotherapy and combination therapy in patients with hypertension.[24-29]
    - Currently, there are no generic single-entity or combination renin inhibitors available.

References

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Therapeutic Class Review
Renin Inhibitors and Combination Products

Overview/Summary

Aliskiren (Tekturna®) is the only single entity direct renin inhibitor available in the United States (U.S.) and 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. that combine the direct renin inhibitor, aliskiren, with other blood pressure-lowering medications from different therapeutic classes including thiazide diuretics, calcium channel blockers and angiotensin II receptor blockers (ARBs). These products include aliskiren/amlodipine (Tekamlo®), aliskiren/amlodipine/hydrochlorothiazide (Amturnide®), aliskiren/hydrochlorothiazide (Tekturna HCT®) and aliskiren/valsartan (Valturna®) and all are FDA-approved for the treatment of hypertension.[1-5] Currently, no combination renin inhibitor is available generically.

In late 2011, the manufacturer of aliskiren, Novartis AG, announced termination of the Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints (ALTITUDE) trial. Investigators reported an increased incidence of non-fatal stroke, renal complications, hyperkalemia and hypotension in the aliskiren treatment arm when added to standard care in patients with type 2 diabetes and concomitant renal impairment. Novartis AG will cease promotion of aliskiren-containing products for use in combination with an angiotensin converting enzyme (ACE)-inhibitor or angiotentin II receptor blocker (ARB).[6] As a result the American Association of Clinical Endocrinologists recommends that physicians transition away from the use of aliskiren in combination with ACE inhibitor or ARB's in patients with diabetes and chronic kidney disease.[7]

The renin-angiotensin-aldosterone system (RAAS) is the most important component in the homeostatic regulation of blood pressure.[8] Renin catalyzes the conversion of angiotensinogen to angiotensin I, which is the first and rate-limiting step of the RAAS.[8-10] 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.[10] Angiotensin II exerts other detrimental cardiovascular effects including hypertrophy, inflammation, remodeling and thrombosis. Angiotensin II also inhibits renin release through a negative feedback mechanism. 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.[11]

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.[11]

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 angiotensin-1 (AT_1) receptor in tissues including vascular smooth muscle and the adrenal gland. Its mechanism of action is not dependent on the synthesis of angiotensin II.[11]

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.[12] 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[1-5]

Generic Name	Treatment of Hypertension Either Alone or in Combination with Other Antihypertensive Agents	Treatment of Hypertension to Lower Blood Pressure	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/ hydrochloro-thiazide		✔			
Aliskiren/ hydrochloro-thiazide			✔	✔	
Aliskiren/ valsartan			✔	✔	✔

Pharmacokinetics

The pharmacokinetic properties of the single-entity renin inhibitors and the individual components of the combination renin inhibitors are outlined in Table 3.

Table 3. Pharmacokinetics[1-5,13]

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
Hydrochloro-thiazide	Not reported	68	Not metabolized	No	Not reported	5.8 to 18.9
Valsartan	10 to 35	95	Liver	No	13	12

Clinical Trials

There are limited studies comparing aliskiren to other antihypertensive agents, including the angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. These studies have generally demonstrated similar efficacy when administered in comparable doses and frequencies.[15-19] In general, the incidence of side effects was also similar between treatment groups. 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] A second study by Zhu et al showed that after eight weeks of treatment, aliskiren was noninferior to ramipril in regard to antihypertensive effects on mean sitting diastolic blood pressure. [21]Schmieder et al compared monotherapy with aliskiren to monotherapy with hydrochlorothiazide and demonstrated significantly lower systolic and diastolic blood pressures at weeks 6 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.[22]

Clinical studies 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.[22-29] Drummond et al compared daily aliskiren/amlodipine 150 mg/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.[27] In separate studies, the combination of aliskiren/hydrochlorothiazide was shown to be significantly more effective than hydrochlorothiazide and aliskiren monotherapy at reducing systolic blood pressure after 8 and 12 weeks, respectively (P<0.0001 compared to monotherapy in both studies). Similarly, greater improvements in diastolic blood pressure were also achieved with aliskiren/ hydrochlorothiazide in both studies compared to treatment with monotherapy (P<0.0001 compared to monotherapy in both studies). [30,31] In a study by Ferdinand et al, patients randomized to receive treatment with aliskiren/hydrochlorothiazide or amlodipine monotherapy experienced a reduction in systolic blood pressure from baseline to week eight, but no differences were observed between treatments (-28.6 vs -28.1 mm Hg for aliskiren/hydrochlorothiazide and amlodipine, respectively; P=0.80).[32] In a short term, open-label study, patients unable to achieve their goal blood pressure with olmesartan/amlodipine 40/10 mg were switched to aliskiren/amlodipine 300/10 mg and achieved a significant reduction in mean sitting diastolic blood pressure over four weeks (P<0.001). Moreover, the antihypertensive effect of adding hydrochlorothiazide 12.5 mg to the aliskiren/amlodipine 300/10 mg regimen was demonstrated by further reducing mean sitting diastolic blood pressure compared to combination therapy with aliskiren/amlodipine alone over four weeks of therapy (P<0.001).[28]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Oh et al[33] Aliskiren 150 mg, 300 mg or 600 mg QD vs placebo	DB, MC, PC, PG, RCT Men and women 18 years of age and older with mild-to-moderate essential hypertension (DBP ≥95 and <110 mm Hg)	N=672 8 weeks	Primary: Change in mean sitting DBP 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	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. 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. 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. 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). 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). 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. 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%).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Kushiro et al[15] Aliskiren 75 mg, 150 mg or 300 mg QD vs placebo	DB, MC, PC, PG, RCT 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)	N=455 8 weeks (active treatment)	Primary: Change in mean sitting DBP 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	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). 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). 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). 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. 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.
Musini et al[16] Aliskiren 75 mg, 150 mg, 300 mg or 600 mg vs placebo	MA Patients 18 years of age and older with mild to moderate hypertension	N=3,694 Varying duration (2 to 4 week run-in period, 4 to 8 week treatment period)	Primary: Change from baseline in trough and/or peak SBP and DBP compared to placebo Secondary: Change in standard deviation compared to placebo, change	Primary: Aliskiren was “superior” to placebo in lowering mean sitting SBP and DBP (*P* value not reported). Secondary: End of treatment standard deviation was similar in the placebo and aliskiren arms. No data were provided at the week-eight endpoint for change in heart rate. No trials reported on pulse pressure at baseline or endpoint.

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	No significant difference between aliskiren and placebo was observed in withdrawals due to adverse events. No trials reported the incidence of angioedema. One trial reported 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%). 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.
Villa et al[34] Aliskiren 75 mg, 150 mg, 300 mg QD vs placebo	DB, MC, PC, RCT Patients 65 years of age and older with essential hypertension (defined as MSSBP ≥150 mm Hg and <180 mm Hg and MSDBP <110 mm Hg)	N=754 8 weeks	Primary: Change in mean sitting SBP from baseline to week eight Secondary: Change in mean sitting DBP from baseline to week eight, proportion of patients achieving BP control (SBP/DBP <140/90 mm Hg), change in 24-hour ambulatory systolic BP and diastolic BP from baseline	Primary: All three doses of aliskiren provided a significantly greater LS mean reduction in SBP from baseline at week eight compared to placebo (-14, -15 and -13 mm Hg vs -8 mm Hg for aliskiren 300, 150 and 75 mg, respectively, compared to placebo; *P*<0.01 for all aliskiren groups). Secondary: The reductions in DBP with all aliskiren doses were significantly greater than those with placebo, with additional reductions of -2, -3 and -3 mm Hg with the 75, 150 and 300 mg aliskiren doses, respectively (*P* <0.05 for all aliskiren groups). A higher percentage of patients achieved BP control (<140/90 mm Hg) after eight weeks with aliskiren treatment compared to placebo. Blood pressure control rates with aliskiren 150 and 300 mg were significantly higher than the placebo group (37.2 and 38.2 vs 23.9%, respectively; *P* <0.01). Although the aliskiren 75 mg treatment group was associated with higher control rates, compared to placebo, this difference did not reach statistical significant (32.8%). The LS mean reductions from baseline in ambulatory SBP were significantly greater with all doses of aliskiren compared to placebo (-4, -5 and -5 mm Hg vs -1 mm Hg with aliskiren 75, 150 and 300 mg, respectively; *P*<0.05 for all). The LS reductions in ambulatory DBP were also significantly greater with both the aliskiren 75 and 150 mg doses (but not 300 mg) compared to placebo (*P*<0.05 for both),
Schmieder et al[17] Aliskiren 150 mg QD	AC, DB, PG, RCT	N=1,124 52 weeks	Primary: Mean sitting DBP	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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
then 300 mg QD after 3 weeks vs HCTZ 12.5 mg QD then 25 mg QD after 3 weeks vs placebo, then either aliskiren 300 mg QD or HCTZ 25 mg QD after 6 weeks	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		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	At week 12, aliskiren was statistically "superior" to HCTZ in reducing mean sitting DBP (*P*<0.001). Secondary: At week six, both aliskiren and HCTZ were "superior" to placebo in lowering mean sitting SBP (*P*<0.0001). At week 12, aliskiren was statically "superior" to HCTZ in reducing mean sitting SBP (*P*<0.001). Aliskiren provided a significantly greater BP response and BP control rates compared to HCTZ (*P*<0.001). 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). 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). 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 between the groups was observed at week 52 in mean sitting SBP. Responder rates were significantly higher with aliskiren compared to HCTZ at week 26 and week 52 (*P*<0.05 and *P*<0.01 respectively). The proportion of patients experiencing adverse effects was similar between groups.
Schmieder et al[19] Aliskiren 150 mg QD then 300 mg QD after 3 weeks	AC, DB, PG, RCT Patients 18 years of age and older with	N=1,124 52 weeks	Primary: Mean sitting DBP Secondary: Mean sitting SBP at week 26, mean	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). Secondary: At week 52, aliskiren resulted in significantly greater mean sitting DBP reductions

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs HCTZ 12.5 mg QD then 25 mg QD after 3 weeks vs placebo, then either aliskiren 300 mg QD or HCTZ 25 mg QD after 6 weeks Subgroup analysis of Schmieder et al[21] in obese patients.	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		sitting DBP and SBP at week 52, proportion of patients with response to treatment, BP control at weeks 26 and 52, and safety	compared to HCTZ (*P*<0.001). BP response rates were significantly greater with aliskiren compared to HCTZ at both week 12 and week 52 (*P*<0.05). 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).
Persson et al[35] Aliskiren 300 mg QD vs irbesartan 300 mg QD vs aliskiren 300 mg QD plus irbesartan 300 mg QD vs placebo	DB, RCT, XO Adult patients with hypertension, type 2 diabetes and albuminuria (>100 mg/day)	N=26 Four 2 month XO treatment periods	Primary: Albuminuria Secondary: 24-hour BP, glomerular filtration rate, biomarkers, and renin angiotensin-aldosterone system components	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. Combination therapy reduced albuminuria significantly more compared to placebo and either monotherapy group (*P*≤0.028). Secondary: Systolic/diastolic 24-hour BP was significantly reduced in all treatment groups compared to placebo (*P*≤0.009). No significant difference was observed between the irbesartan and combination therapy group. Glomerular filtration rate was significantly reduced in all treatment groups compared to placebo (*P*≤0.037). No significant difference was observed between the irbesartan and combination therapy group. 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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Strasser et al[36] Aliskiren 150 mg to 300 mg QD vs lisinopril 20 mg to 40 mg QD HCTZ may be added to aliskiren 300 mg or lisinopril 40 mg if additional BP control was required. The study did not specifically analyze the effects of HCTZ on either treatment regimen.	AC, DB, DD, MC, PG, RCT Men and women with uncomplicated severe hypertension (mean sitting DBP 105 to 119 mm Hg)	N=183 8 weeks	Primary: Safety Secondary: Change in mean sitting DBP and SBP and percentage of responders	Primary: 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 *P* values were reported for this endpoint). Secondary: 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; *P* values not reported). 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; *P* values not reported).
Duprez et al[14] (abstract) Aliskiren 150 mg to 300 mg QD vs ramipril 5 mg to 10 mg QD HCTZ 12.5 mg to 25 mg QD was allowed as add-on therapy at week 12 and amlodipine 5 to 10	AC, DB, PG, RCT Patients 65 years of age and older with SBP ≥140 mm Hg	N=901 36 weeks	Primary: Mean sitting SBP at week 12 Secondary: Mean sitting DBP, BP control, and patients requiring add-on therapy with HCTZ or amlodipine	Primary: 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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg QD at week 22.				
Andersen et al[18] Aliskiren 150 mg to 300 mg QD vs ramipril 5 mg to 10 mg QD 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 Hg), and safety	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 6 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 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. 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 (*P* values not reported).
Zhu et al[21] Aliskiren 75 mg, 150 mg, 300 mg QD	AC, DB, MC, PG, RCT Patients aged	8 weeks N=1,613	Primary: Change in mean sitting DBP from baseline to week	Primary: After eight weeks, the least square mean reductions from baseline in DBP were -11.63, -10.04 and -10.66 mm Hg for aliskiren doses of 300, 150 and 75 mg, respectively, vs ramipril (-9.19 mm Hg). Pairwise comparisons showed that all

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs ramipril 5 mg QD	18 years or older with uncomplicated essential hypertension and MSDBP ≥90 and <110 mm Hg at the visit immediately before randomization, MSDBP ≥95 and <110 mm Hg at the time of randomization and absolute difference of ≤10 mm Hg in MSDBP after the run-in period		eight Secondary: Change in mean sitting SBP from baseline to week eight in the proportion of patients achieving BP control (<140/ 90 mm Hg) and the proportion of patients achieving BP response (DBP <90 mm Hg or reduction of ≥10 mm Hg from baseline in DBP), PP and MAP	doses of aliskiren were noninferior to ramipril (treatment difference, -2.44; 95% CI, -3.63 to -1.25; *P*<0.001, -0.86; 95% CI, -2.06 to -0.34; *P*<0.001 and -1.48; 95% CI, -2.67 to -0.28; *P*<0.001) for aliskiren 300, 150 and 75 mg, respectively). Secondary: The reductions in SBP were greater in the aliskiren treatment groups compared to the ramipril group after eight weeks of treatment; however, only the aliskiren 300mg dose was shown to be significantly more effective compared to ramipril 5 mg (*P*=0.0014). By week eight, the proportion of patients who had their BP controlled to <140/90mm Hg was higher in all three aliskiren treatment groups (52.29, 48.11 and 45.68% with 300, 150 and 75 mg, respectively) compared to the 5 mg ramipril treatment group (43.65%); however, the difference was only significant for the aliskiren 300 mg treatment group (*P*=0.0177). The BP responder rate was higher with all three aliskiren doses (67.89, 59.75 and 59.57% for the 300, 150 and 75 mg doses, respectively) compared to ramipril (53.87%); however, the difference was only significant with the aliskiren 300 mg treatment group (*P*<0.0001). At week eight, the LS mean changes in PP from baseline were -2.69, -1.95 and -1.66 mm Hg for aliskiren 300, 150 and 75 mg, respectively, compared to ramipril (-2.19 mm Hg; *P* values not reported). The decrease in MAP was greater in all aliskiren treatment groups compared with the ramipril treatment group. The LS mean changes in MAP from baseline were -12.62, -10.74 and -11.12 mm Hg for 300, 150 and 75 mg aliskiren doses, respectively, compared to -9.9 mm Hg for ramipril. Only the aliskiren 300 mg treatment group lowered MAP significantly more than ramipril (*P*<0.0001).
Gradman et al[37] Aliskiren 150 mg, 300 mg, or 600 mg QD vs	DB, MC, PC, PG, RCT Men and women, 18 years of age or	N=652 13 weeks (8 weeks active treatment)	Primary: Change in mean sitting DBP and SBP Secondary:	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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
irbesartan 150 mg QD vs placebo	older, with mild-to-moderate essential hypertension (mean sitting DBP ≥95 and <110 mm Hg)		Proportion of patients achieving BP control (<140/90 mm Hg), and safety	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. 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). 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). 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 in all groups.
Stanton et al[38] Aliskiren 37.5 mg, 75 mg, 150 mg, or 300 mg QD vs losartan 100 mg QD	AC, DB, MC, PG, RCT Men and women 21 to 70 years of age with mild-to-moderate hypertension (SBP ≥140 mm Hg)	N=226 4 weeks	Primary: Change in daytime ambulatory SBP Secondary: Changes in clinic SBP and DBP, plasma renin activity, plasma aliskiren levels, and adverse events	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; *P*=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 (*P* values not reported). 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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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; *P*=0.0008). By contrast, plasma renin activity increased by 110% with losartan. 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 *P* value reported). There was no increase in the number of adverse events when increasing the dose of aliskiren.
Wiysonge et al[39] Other antihypertensive therapies (i.e., placebo, diuretics, calcium channel blockers or renin-angiotensin system inhibitors) vs β-blockers (atenolol, metoprolol, oxprenolol* or propranolol)	MA 13 RCTs evaluating patients ≥18 years of age with hypertension	N=91,561 Duration varied	Primary: All-cause mortality Secondary: Stroke, coronary heart disease, cardiovascular death, total cardiovascular disease, adverse reactions	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; *P* value not reported), diuretics (RR, 1.04; 95% CI, 0.91 to 1.19; *P* value not reported) or renin-angiotensin system inhibitors (RR, 1.10; 95% CI, 0.98 to 1.24; *P* 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; *P*=0.04). 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 (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). 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). 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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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.
Parving et al[40] (AVOID) Losartan 100 mg daily plus aliskiren 150 mg daily for 3 months then 300 mg for an additional 3 months vs losartan 100 mg plus placebo	DB, MC, PC, RCT Hypertensive patients who were 18 to 85 years of age with type 2 diabetes and nephropathy	N=599 6 months	Primary: Reduction in albumin:creatinine ratio at six months Secondary: BP reductions and adverse events	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). 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). The total numbers of adverse and serious adverse events were similar in the groups.
Jordan et al[20] Aliskiren 150 mg QD vs amlodipine 5 mg QD vs irbesartan 150 mg QD vs placebo After four weeks, doses	DB, DD, MC, PG, RCT Obese men and women (BMI ≥30 kg/m^2) 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	N=489 16 weeks (4 weeks of HCTZ monotherapy and 12 weeks of combination therapy)	Primary: Change in mean sitting DBP with aliskiren 300 mg plus HCTZ vs HCTZ alone at eight weeks Secondary: Comparisons of mean sitting DBP and SBP with aliskiren plus HCTZ vs the other treatment groups, percentage of responders (mean	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). 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). 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). 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
of aliskiren, irbesartan and amlodipine were doubled and treatment was continued for an additional 8 weeks. All patients continued to receive HCTZ 25 mg QD.	treatment with HCTZ 25 mg		sitting DBP <90 mm Hg or ≥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*=0.0001) but not statistically different than amlodipine plus HCTZ (*P*>0.05) and irbesartan plus HCTZ (*P*>0.05). 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). 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%; *P* values not reported), largely due to a higher rate of peripheral edema (11.1 vs 0.8 to 1.6%; *P* values not reported).
Ferdinand et al[32] Aliskiren/HCTZ 150 mg/ 12.5 mg QD for one week, then force titrated to receive 300 mg/ 25 mg QD vs amlodipine 5 mg QD for one week, then force titrated to receive 10 mg QD	AC, DB, DD, MC, PRO, RCT African American men and women, 18 years and older with stage 2 hypertension (defined as mean sitting systolic BP [MSSBP] ≥160 mm Hg and <200 mm Hg	8 weeks N=332	Primary: Change from baseline in mean sitting SBP Secondary: Change from baseline in mean sitting DBP, change in mean sitting pulse pressure (MSPP), percentage of patients achieving BP control (defined as SBP <140 mm Hg and DBP <90 mm Hg), safety and tolerability	Primary: Patients randomized to receive either treatment regimen experienced a reduction in SBP from baseline to week eight, but there were no significant differences between the treatments (-28.6 vs -28.1 mm Hg for aliskiren/HCTZ and amlodipine, respectively; *P*=0.80). Secondary: Both treatment regimens were associated with significant reductions from baseline in DBP by the end of treatment, although no significant differences were reported between the treatment arms (-9.4 vs -10.9 mm Hg for aliskiren/HCTZ and amlodipine, respectively; *P*=0.20). The changes in MSPP also appear to be similar between patients receiving combination therapy and those receiving monotherapy with amlodipine (-19.16 vs -17.31 mm Hg, respectively; *P* value not reported). The percentage of patients achieving BP control (<140/90 mm Hg) by the end of the study was 53.8% in the aliskiren/HCTZ arm and 48.7% in the amlodipine arm (*P* value not reported). The percentage of patients in both groups who reported at least one adverse event was 44.6% in the aliskiren/HCTZ group and 34.3% of patients in the amlodipine monotherapy group. The adverse events experienced by ≥2% of patients receiving either treatment

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				regimen were headache, diarrhea, nausea, hypokalemia, nasopharyngitis, upper respiratory tract infection, peripheral edema and pain. The incidence of these adverse events was similar between treatment groups. Most adverse events were considered to be of mild or moderate severity and most were, in the investigator's opinion, treatment-related. The overall incidence of study-related adverse events was 10.8% in the aliskiren/HCTZ group and 6% in the amlodipine group.
Basile et al[30] Aliskiren/HCTZ 150 mg/ 12.5 mg QD for 1 week, and then double the doses for 7 weeks vs HCTZ 12.5 mg QD 1 for week, and then double the doses for 7 weeks	AC, DB, MC, PG, RCT Men and women 55 years and older with stage 2 systolic hypertension, defined as mean sitting SBP (MSSBP) ≤160 and <200 mm Hg	8 weeks N=451	Primary: Change from baseline to week-four in mean sitting SBP Secondary: Change from baseline to week-four in mean sitting DBP, change in mean sitting SBP and mean sitting DBP from baseline to week-eight, the proportion of patients reaching BP goal (<140/90 mm Hg) at week-four and week-eight	Primary: Treatment with aliskiren/HCTZ provided a significantly greater reduction in SBP from baseline compared to HCTZ monotherapy at week four (-29.6 vs -22.3 mm Hg; *P*<0.0001). Secondary: The mean reduction in DBP was also significantly greater with aliskiren/HCTZ compared to HCTZ monotherapy after four weeks of treatment (*P*<0.005). The improvements in SBP and DBP remained significantly greater after eight weeks of treatment in the aliskiren/HCTZ group compared to the HCTZ monotherapy group (-11.2 vs -7.6 mm Hg and -33.2 vs -25.7 mm Hg for changes in DBP and SPB, respectively; *P*<0.0001 for both comparisons). At week four, more patients treated with a combination of aliskiren/HCTZ were able to achieve their goal blood pressure target compared to the HCTZ monotherapy group (51.1 vs 33.3%; *P*=0.0001). This difference remained significant through week eight of treatment (62.2 vs 39.2%; *P*<0.0001).
Townsend et al[29] Aliskiren/HCTZ 150 mg/ 12.5 mg QD for 1 week, and then double the doses for 7 weeks vs	AC, DB, MC, PG, RCT Patients 18 years and older with stage 2 systolic hypertension and type 2	8 weeks N=860	Primary: Change from baseline in mean sitting SBP at eight weeks Secondary: Change from baseline at eight	Primary: After eight weeks of treatment, aliskiren/HCTZ 300/12.5 mg combination therapy reduced SBP significantly more than amlodipine 10 mg (LS mean change, -28.8 vs -26.2 mm Hg; *P*<0.0001 for noninferiority, *P*<0.05 for "superiority"). Secondary: There were similar reductions in DBP after eight weeks with aliskiren/HCTZ compared to amlodipine (*P* value not reported). For patients with isolated stage two systolic hypertension, aliskiren/HCTZ treatment significantly reduced SBP

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
amlodipine 5 mg QD 1 for week, and then double the doses for 7 weeks	diabetes mellitus (HbA_{1c} ≤9%); treated with an antidiabetic regimen or on a stable diet and exercise program for ≥4 weeks before screening)		weeks in mean sitting SBP in patients with isolated stage two systolic hypertension (baseline DBP <90 mm Hg), change in DBP in the overall study population and in the subgroup of patients with baseline DBP ≥90 mm Hg, the percentage of patients who achieved BP control (<130/80 mm Hg) and percentage of patients with edema	compared amlodipine monotherapy (-29.2 vs 24.8 mm Hg; *P*<0.01). Patients with a DBP of ≥90 mm Hg at baseline showed a numerically greater reduction in DBP with aliskiren/HCTZ treatment compared to amlodipine (-12.3 vs -11.6 mm Hg; *P* value not reported), however, the difference was not significant. The proportion of patients who achieved BP control (<130/80 mm Hg) after eight weeks of treatment was significantly higher with aliskiren/HCTZ combination therapy compared to amlodipine monotherapy (23.2 vs 13.8%; *P*<0.0001). Peripheral edema was more common with amlodipine monotherapy (16.2%) compared to aliskiren/HCTZ combination therapy (2.1%). In the amlodipine group, 12 patients (2.8%) discontinued because of peripheral edema and two (0.5%) because of edema. There were no discontinuations related to edema or peripheral edema with aliskiren/HCTZ. Between-treatment comparison showed that edema, identified either by patient report or physical examination, occurred significantly more frequently in the amlodipine group than the aliskiren/HCTZ group (17.6 vs 2.6%; *P*<0.0001).
Drummond et al[27] Aliskiren/amlodipine 150 mg/ 5 mg QD vs amlodipine 5 mg QD vs amlodipine 10 mg QD	AC, DB, MC, PG, RCT Patients 18 years of age and older with mild to moderate hypertension	N=545 6 weeks	Primary: Change in DBP at six weeks Secondary: SBP, comparison of SBP and DBP reductions between combination therapy group and amlodipine 10 mg group, proportion of patients responding	Primary: DBP reduction was significantly greater in the combination therapy group compared to those in the amlodipine 5 mg group (*P*<0.0001). Secondary: SBP reduction was significantly greater in the combination therapy group 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Patients not responding to amlodipine 5 mg QD at the end of four week single-blind run-in period received combination therapy, continuation of amlodipine 5 mg QD or titration to amlodipine 10 mg QD.			to treatment, and proportion of patients achieving BP control	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[22] Aliskiren 75 mg, 150 mg or 300 mg QD vs HCTZ 6.25 mg, 12.5 mg or 25 mg QD vs aliskiren plus HCTZ (every dose combination except aliskiren 300 mg and HCTZ 6.25 mg) QD vs placebo	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 successful response (DBP <90 mm Hg or a ≥10 mm Hg), proportion achieving BP control (<140/90	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). 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. BP reductions were related to the doses of both aliskiren and HCTZ.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			mm Hg), plasma renin activity, renin concentrations, and safety	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). 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. 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. 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 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.
Black et al[31] Aliskiren/HCTZ 150 mg/12.5 mg QD	AC, DB, MC, PG, RCT Men and women	12 weeks N=688	Primary: Change from baseline in mean systolic blood	Primary: Aliskiren/HCTZ treatment was associated with significantly greater mean reductions from baseline in SBP compared aliskiren monotherapy by week 12 (-30.0 vs -20.3 mm Hg; *P*<0.0001). Mean reductions in DBP were also significantly

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs aliskiren 150 mg QD This study included an early forced-titration step. After one week, the initial doses were doubled and treatment continued for a further 11 weeks.	aged 18 years and older with SBP ≥160 mm Hg and <180 mm Hg		pressure (SBP) Secondary: Mean change in SBP from baseline to week 8, DBP at weeks 8 and 12, proportions of patients achieving BP goal (<140/90 mm Hg [<130/80 mm Hg for patients with DM]) and those considered ''responders'' (SBP <140 mm Hg [<130 mm Hg for patients with DM] or ≥20 mm Hg decrease) were assessed at weeks 8 and 12	greater with aliskiren/HCTZ compared with aliskiren alone (P<0.0001). Secondary: After eight weeks, patients receiving combination treatment with aliskiren/HCTZ experienced greater improvements in SBP compared to patients randomized to aliskiren monotherapy (-29.6 vs -19.0 mm Hg; *P*<0.0001). At week-eight, treatment with aliskiren/HCTZ was more effective than aliskiren alone for reducing DBP (-13.7 vs -8.0 mm Hg; *P*<0.0001). By week 12, combination therapy with aliskiren/HCTZ continued to be significantly more effective than aliskiren monotherapy at reducing DBP (-12.6 vs -8.2 mm Hg; *P*<0.0001). After eight weeks, more patients receiving combination treatment with aliskiren/HCTZ were able to achieve a blood pressure target of <140/90 mm Hg (<130/80 mm Hg for patients with DM) compared to patients receiving aliskiren alone (53.5 vs 30.4%; *P*<0.0001). At 12 weeks, more patients in the combination treatment groups continued to meet their blood pressure goals compared to aliskiren monotherapy, although slight increased occurred since week-eight (54.6 vs 32.3%; *P*<0.0001)
Blumenstein et al[41] (abstract) Aliskiren/HCTZ 150 mg/ 25 mg QD vs aliskiren/HCTZ 300 mg/ 25 mg QD vs HCTZ 25 mg QD	DB, RCT Patients with hypertension not responding to 4 weeks of monotherapy with HCTZ 25 mg QD	N=722 8 weeks	Primary: Mean sitting DBP and SBP Secondary: BP control rates	Primary: Mean sitting DBP and SBP reductions were significantly greater in both combination therapy groups compared to HCTZ monotherapy (*P*<0.001). Aliskiren/HCTZ 300/25 mg produced significantly greater reductions compared to the aliskiren/HCTZ 150/25 mg group (*P*<0.05). Secondary: Both combination treatment groups produced significantly greater BP control rates compared to HCTZ monotherapy (*P*<0.001). Aliskiren/HCTZ 300/25 mg produced significantly greater BP control rates compared to the aliskiren/HCTZ 150/25 mg group (*P*<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Geiger et al[42] Aliskiren/HCTZ 150 mg/ 25 mg QD for 4 weeks then 300 mg/ 25 mg QD for 4 weeks vs valsartan/HCTZ 160mg /25 mg QD for 4 weeks then 320/25 mg QD for 4 weeks vs aliskiren/valsartan/HCTZ 150 mg/160 mg/25 mg QD for 4 weeks then 300 mg/320 mg/25 mg QD for 4 weeks vs HCTZ 25 mg QD for 8 weeks Patients not responding to HCTZ 25 mg QD after four weeks were randomized to one of the above treatment regimens.	AC, DB, PG, RCT Patients 18 years of age and older with mild to moderate hypertension	N=641 8 weeks	Primary: DBP at week eight Secondary: SBP at week eight, changes in DBP and SBP at week four, and proportion of patients achieving BP control	Primary: The aliskiren/valsartan/HCTZ group showed significantly greater reductions in DBP at week eight compared to the other groups (*P*<0.01). Secondary: The aliskiren/valsartan/HCTZ group showed significantly greater reductions in SBP at week eight compared to the other groups (*P*<0.01). 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). 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). 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). Both the aliskiren/HCTZ and valsartan/HCTZ groups demonstrated significantly better rates of BP control compared to the HCTZ monotherapy group at week four and eight (*P* values not reported).
Obrien et al[23] Aliskiren 150 mg QD for	3 OL studies Men and women	N=67 6 to 9 weeks	Primary: Change in daytime systolic ABPM with	Primary: Aliskiren coadministered with HCTZ (*P*=0.0007) or ramipril (*P*=0.03) led to significantly greater reductions in daytime systolic ABPM compared to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
3 weeks, if ABPM remained ≥135/85 mm Hg, HCTZ 25 mg QD was added for an additional 3 weeks vs irbesartan 150 mg QD for 3 weeks, then aliskiren 75 mg QD added for 3 weeks, then aliskiren 150 mg QD added for 3 weeks vs ramipril 5 mg QD for 3 weeks, then aliskiren 75 mg QD added for 3 weeks, then aliskiren 150 mg QD added for 3 weeks	18 to 80 years of age with ambulatory SBP ≥140 and ≤180 mm Hg without treatment		combination therapy compared to monotherapy Secondary: Change in daytime diastolic ABPM, nighttime systolic and diastolic ABPM, daytime and nighttime heart rates, and plasma renin activity	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 (*P* value not reported). Secondary: Aliskiren plus HCTZ significantly lowered daytime diastolic ABPM compared to aliskiren monotherapy (*P*=0.0006). Changes in nighttime systolic and diastolic ABPM followed similar trends but did not achieve statistical significance (*P*=0.06 and *P*=0.09, respectively). No changes in heart rate were observed with either aliskiren regimen. Aliskiren added to irbesartan did not significantly change diastolic ABPM compared to irbesartan monotherapy; however, nighttime systolic and diastolic ABPM were significantly reduced (all *P*<0.05). No changes in heart rate were observed with either irbesartan regimen. Mean diastolic ABPM was significantly decreased with the addition of aliskiren 150 mg (*P*<0.05) but not aliskiren 75 mg (*P* value not reported) to ramipril monotherapy. Both aliskiren doses significantly decreased nighttime systolic and diastolic ABPM (all *P*<0.05). No changes in heart rate were observed with either ramipril regimen. 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.
Oparil et al[24] Aliskiren 150 mg QD for 4 weeks followed by 300 mg QD for 4 weeks vs valsartan 160 mg QD for 4 weeks followed by 320	DB, MC, PC, PG, RCT Men and women ≥18 years of age with stage 1 to 2 essential hypertension (mean sitting DBP 95 to 109	N=1,797 8 weeks (4 weeks with forced titration to double the dose to the maximum recommende	Primary: Change in mean sitting DBP Secondary: Change in mean sitting SBP, proportion of patients achieving a successful	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). Secondary: At week eight, the combination of aliskiren 300 mg plus valsartan 320 mg lowered

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg QD for 4 weeks vs aliskiren/valsartan 150 mg/160 mg QD for 4 weeks followed by 300 mg/320 mg QD for 4 weeks vs placebo	mm Hg and 8-hour ambulatory DBP ≥90 mm Hg)	d dose for another 4 weeks)	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	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). 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). 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). 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*<0.0001). The greater reductions in ambulatory BP with aliskiren plus valsartan were maintained throughout the entire 24-hour dosing interval. 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. 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). The combination of aliskiren and valsartan (-31%; *P*<0.0001) and valsartan monotherapy (-25%; *P*=0.0007) provided significantly greater reductions in plasma

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				aldosterone concentration than did placebo (+7%), while aliskiren monotherapy had no significant effect (-5.9%; *P*=0.1059). Rates of adverse events and laboratory abnormalities were similar in all groups.
Yarows et al[25] Aliskiren 150 mg QD for 4 weeks followed by 300 mg QD for 4 weeks vs valsartan 160 mg QD for 4 weeks followed by 320 mg QD for 4 weeks vs aliskiren/valsartan 150 mg/160 mg QD for 4 weeks followed by 300 mg/320 mg QD for 4 weeks vs placebo This is a post-hoc analysis from Oparil et al[25] of patients with stage 2 hypertension.	PG, RCT 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)	N=1,797 8 weeks	Primary: Change in mean sitting DBP 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)	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). 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). DBP and SBP reductions in both monotherapy groups were significantly greater compared to placebo (*P*<0.0001). 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 compared to both monotherapy groups and placebo (*P*≤0.044). 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.
Pool et al[26] Aliskiren 75 mg, 150 mg or 300 mg QD	DB, MC, PC, PG, RCT Men and women	N=1,123 8 weeks	Primary: Change in mean sitting DBP	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,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs valsartan 80 mg, 160 mg or 320 mg vs aliskiren/valsartan 75 mg, 150 mg or 300 mg/80 mg, 160 mg or 320 mg, respectively vs valsartan/HCTZ 160 mg/12.5 mg vs placebo	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)		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	respectively). Secondary: Aliskiren 300 mg significantly (*P*<0.0001) lowered mean sitting SBP compared to placebo. 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. 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. 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. 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. 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.
Dietz et al[43] Aliskiren 150 mg QD for 6 weeks, followed by	DB, MC, RCT Patients ≥18 years of age	N=694 12 weeks	Primary: Change in mean sitting DBP, mean sitting SBP, mean	Primary: At week 12, combination therapy lowered mean sitting SBP by 14.1±0.6 mm Hg, a significantly greater reduction compared to that achieved with aliskiren monotherapy (least squares mean difference, -2.9 mm Hg; 95% CI, -4.5 to -1.3;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
300 mg QD vs atenolol 50 mg QD, for 6 weeks, followed by 100 mg QD vs aliskiren 150 mg QD plus atenolol 50 mg QD for 6 weeks, followed by aliskiren 300 mg QD plus atenolol 100 mg QD All patients entered a two week washout period, followed by a two to four week SB, placebo, run in period.	with hypertension (mean sitting DBP ≥95 and <110 mm Hg)		pulse pressure and pulse rate; blood pressure control (<140/90 mm Hg) rates Secondary: Not reported	*P*<0.001), but not atenolol monotherapy (-0.5 mm Hg; 95% CI, -2.1 to 1.1; *P*=0.545). Reductions were significantly greater with atenolol monotherapy compared to aliskiren monotherapy (-2.4 mm Hg; 95% CI, 0.8 to 4.0; *P*=0.003). At week 12, combination therapy lowered mean sitting SBP by 17.3±1.1 mm Hg, a significantly greater reduction compared to that achieved with aliskiren monotherapy (least squares mean difference, -2.9 mm Hg; 95% CI, -5.7 to -1.0; *P*=0.039) and atenolol monotherapy (-3.0 mm Hg; 95% CI, -5.8 to -0.2; *P*=0.034). There was no difference in the reductions in mean sitting SBP achieved with aliskiren and atenolol monotherapy (-0.1 mm Hg; 95% CI, -2.9 to 2.7; *P*=0.954). At six weeks, combination therapy decreased blood pressure to a significantly larger extent compared to aliskiren monotherapy (14.5/12.3 vs 10.8/9.2 mm Hg; *P*=0.005 for mean sitting SBP and *P*<0.001 for mean sitting DBP). Combination therapy only achieved significantly larger reductions in mean sitting SBP compared to atenolol monotherapy (-14.5/-12.3 vs -11.3/-12.5 mm Hg; *P*=0.013 for mean sitting SBP and *P*=0.798 for mean sitting DBP). At week 12, mean pulse pressure was reduced by approximately 3 mm Hg with combination therapy and aliskiren monotherapy (*P* values not reported). Atenolol monotherapy had no notable effect on pulse pressure. At week 12, a significant mean reduction in pulse rate >10 BPM was achieved with combination therapy and atenolol monotherapy (*P*<0.001 vs aliskiren monotherapy). Aliskiren monotherapy had no notable effect on pulse rate. Rates of blood pressure control at week 12 were higher with combination therapy (51.3%) compared to either aliskiren (36.1%; *P*<0.001) and atenolol (42.2%; *P*=0.009) monotherapies. There was no significant difference in BP control rates between aliskiren and atenolol monotherapies (*P*=0.388). Secondary: Not reported
Axthelm et al[28] Aliskiren/amlodipine	MC, NR, OL Patients 18	Up to 12 weeks	Primary: Change in trough mean sitting DBP	Primary: By the end of treatment in Phase II (four weeks of treatment with aliskiren/amlodipine 300/10 mg), the combination of aliskiren/amlodipine

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
300/10 mg QD (following an inadequate response in Phase I with olmesartan/amlodipine 40/10 mg QD, defined as a mean sitting DBP ≥90 mm Hg) vs aliskiren/amlodipine /HCTZ 300/10/12.5 mg QD (extension phase for non-responders in Phase II with olmesartan/amlodipine 40/10 mg QD, defined as a MSDBP ≥90 mm Hg or trough mean sitting SBP ≥140 mm Hg)	years of age or older with uncomplicated moderate hypertension defined as a mean sitting DBP 100 to 109 mm Hg and mean sitting SBP 160 to 179 mm Hg after a 3-week washout period	N=342	between visits five and six (four weeks of treatment in Phase II), change in mean sitting DBP between visits six and seven (four-week extension phase with the addition of HCTZ) Secondary: Changes in mean sitting SBP, pulse rate, systolic responder rates, diastolic responder rate, the systolic/diastolic normalization rate, and the proportion of patients treated to target (SBP <140 mm Hg and DBP <90 mm Hg), safety and tolerability.	significantly decreased DBP compared to the olmesartan/amlodipine 40/10 mg group (-4.8 mm Hg; *P*<0.001). The addition of HCTZ in Phase III (four weeks of treatment with aliskiren/amlodipine/HCTZ 300/10/12.5 mg) was associated with further reductions in MSDBP compared to treatment with aliskiren/amlodipine 300/10 mg alone (-8.1 mm Hg; *P*<0.001). Secondary: Aliskiren/amlodipine 300/10 mg was associated with a greater reduction in SBP compared to Phase I treatment with olmesartan/amlodipine 40/10 mg (-5.1 mm Hg; *P*<0.001). In the extension phase (Phase III), the SBP was significantly lower following the addition of HCTZ to the treatment regimen compared to aliskiren/amlodipine 300/10 mg alone (-6.7 mm Hg; *P*<0.001). The change in sitting pulse rate was significantly lower during the extension phase (Phase III) following the addition of HCTZ to aliskiren/amlodipine (*P*=0.02). The systolic responder rates (defined as SBP <140 mm Hg or decrease ≥20 mm Hg vs prior visit) were 66.1, 44.4 and 53.8% of patients during Phases I, II and III, respectively (*P* values not reported). The diastolic responder rates (defined as a DBP <90 mm Hg or ≥10 mm Hg decrease compared to previous visit) were 76.1, 51.3 and 76.9% of patients in Phases I, II and III, respectively (*P* value not reported). The systolic normalization rate (defined as SBP <140mm Hg) was 41.3, 43.3 and 52.3% for patients during Phases I, II and III treatment, respectively (*P* value not reported). The diastolic normalization rate (defined as DBP <90 mm Hg) was reported in 76.1, 51.3 and 76.9% of patients receiving antihypertensive treatment in Phases I, II and III, respectively (*P* value not reported). A higher percentage of patients were treated to target blood pressure (SBP <140 mm Hg and DBP <90 mm Hg) in Phase III compared to Phases I and II (46.2 vs 31.3 and 36.4%, respectively (*P* values not reported). The most frequently reported adverse event was peripheral edema, with nine (2.6%) patients affected in Phase I and seven (3.7%) patients in Phase II. Edema occurred in one (0.3%) patient in Phase I and three (1.6%) patients in Phase II. Eczema was reported in three (0.9%) patients in Phase I and one

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				(0.5%) patient in Phase II. All other adverse events occurred only in one or two patients. There were nine (2.6%) patients who discontinued study drug due to an adverse event in Phase I and five (2.7%) patients who discontinued study drug due to an adverse event in Phase II.

Drug regimen abbreviations: HCTZ=hydrochlorothiazide, QD=once daily
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, DD=double-dummy, MA=meta-analysis, MC=multicenter, NR=non-randomized, OL=open-label, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RR=relative risk, SB=single blind, XO=cross-over
Miscellaneous abbreviations: ABPM=ambulatory blood pressure monitoring, BMI=body mass index, BP=blood pressure, BPM=beats per minute, DBP=diastolic blood pressure, DM=diabetes mellitus, HbA_{1c}= glycosylated hemoglobin, mm Hg=millimeters of mercury, LS=least squares, MAP= mean arterial pressure, MSSBP=mean sitting systolic blood pressure, MSDBP=mean sitting diastolic blood pressure, MSPP=mean sitting pulse pressure, PP=pulse pressure, SBP=systolic blood pressure

Special Populations

Table 5. Special Populations[1-5,11,13]

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 that is unavailable for this product. 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 (%)[1,5,11,13]

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/ hydrochloro-thiazide	Aliskiren/ hydro-chloro-thiazide	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.[1-5,11,13]

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. [1-5,11,13]

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. [1-5,11,13]

Routine monitoring of electrolytes and renal function is indicated in diabetic patients concurrently taking aliskiren and angiotensin converting enzyme (ACE) inhibitors. 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, and 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. [1-5,11,13]

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.[5]

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.[2,4]

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.[2,4] Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.[2,4] Lithium should generally not be given with thiazide diuretics.[2,4]

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.[2,4]

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.[5]

Tekturna HCT®
Periodic determinations of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.[2]

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).[3]

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. Patients with hepatic impairment have shown lower valsartan clearance.

Some patients with heart failure have developed increases in blood urea nitrogren, 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.[3]

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.[3]

Black Box Warning[1-5,11,13]

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[1-5,11,13]

Generic Name	Interacting Medication or Disease	Mechanism
Aliskiren	Angiotensin-converting enzyme (ACE) 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 mg 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	Itraconzole 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.
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.
Hydro-	Cisapride	Cisapride is contraindicated in patients receiving thiazide diuretics.

Generic Name	Interacting Medication or Disease	Mechanism
chlorothiazide		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.
Hydro-chlorothiazide	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.
Hydro-chlorothiazide	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.
Hydro-chlorothiazide	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.
Hydro-chlorothiazide	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.
Hydro-chlorothiazide	Loop diuretics (bumetanide, ethacrynic acid, furosemide, torsemide)	Coadministration may lead to greater sodium, potassium and chloride excretion and dieresis. Careful titration with small or intermittent doses is recommended. Monitor for dehydration and electrolyte abnormalities during concurrent use.
Hydro-chlorothiazide	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[1-5,11,13]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Aliskiren	Treatment of hypertension either alone or in combination with other antihypertensive agents: Initial, 150 mg QD; may increase	Safety and efficacy have not been established in pediatric patients	Tablet: 150 mg 300 mg

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	daily dose to 300 mg if blood pressure not adequately controlled	under the age of 18.	
Combination Products			
Aliskiren/ amlodipine	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: Initial, 150 mg/5 mg QD; maximum, 300 mg/10 mg	Safety and efficacy have not been established in pediatric patients under the age of 18.	Tablet: 150 mg/5 mg 150 mg/10 mg 300 mg/5 mg 300 mg/10 mg
Aliskiren/ amlodipine/ hydrochloro-thiazide	Treatment of hypertension to lower blood pressure: Dose QD; maximum, 300 mg/10 mg/25 mg QD	Safety and efficacy have not been established in pediatric patients under the age of 18.	Tablet: 150 mg/5 mg/12.5 mg 300 mg/5 mg/12.5 mg 300 mg/5 mg/25 mg 300 mg/10 mg/12.5 mg 300 mg/10 mg/25 mg
Aliskiren/ hydrochloro-thiazide	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: Initial, 150 mg/12.5 mg QD; maximum, 300 mg/25 mg QD	Safety and efficacy have not been established in pediatric patients under the age of 18.	Tablet: 150 mg/12.5 mg 150 mg/25 mg 300 mg/12.5 mg 300 mg/25 mg
Aliskiren/ valsartan	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: Initial, 150 mg/160 mg QD; maximum, 300 mg/320 mg	Safety and efficacy have not been established in pediatric patients under the age of 18.	Tablet: 150 mg/160 mg 300 mg/320 mg

QD=once daily

Clinical Guidelines

Table 9. Clinical Guidelines

Clinical Guideline	Recommendations
National Heart, Lung, and Blood Institute: **The Seventh Report of The Joint National**	• 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)

Clinical Guideline	Recommendations
Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (2004)[42]	demonstrated to be beneficial in randomized controlled outcome trials • 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

Clinical Guideline	Recommendations
	pregnant or may become pregnant.
World Health Organization/ International Society of Hypertension: **2003 World Health Organization/ International Society of Hypertension Statement on Management of Hypertension (2003)**[43]	• 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).
European Society of Hypertension/ European Society of Cardiology: **2007 Guidelines for the Management of Hypertension (2007)**[41], **Reappraisal of Guidelines on Hypertension Management (2009)**[7]	• 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. • 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

Clinical Guideline	Recommendations
	with a calcium channel blocker. • 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.
National Institute for Health and Clinical Excellence/British Hypertension Society: **Hypertension: Clinical Management of Primary Hypertension in Adults: (2011)**[45]	• Initial therapy in patients <55 years of age should be an ACE inhibitor or an ARB if the patient is intolerant to ACE inhibitors. • Do not combine an ACE inhibitor with an ARB to treat hypertension. • Initial therapy in patients ≥55 years of age should be a calcium channel blocker or for black people of African or Caribbean family origin of any age. If a calcium channel blocker is not suitable, or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic. • If diuretic treatment is to be initiated or changed, offer a thiazide-like diuretic, such as chlorthalidone (12.5 to 25.0 mg daily) or indapamide (1.5 mg modified-release daily or 2.5 mg once) in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide. • Beta-blockers are not a preferred initial therapy for hypertension. However, beta-blockers may be considered in younger people, particularly those with an intolerance or contraindication to ACE inhibitors and ARBs, women of child-bearing potential those with an increased sympathetic drive. • If a second medication is required treatment with a calcium channel blocker in combination with an ACE inhibitor or an ARB should be added. If a calcium channel blocker is not suitable, or if there is evidence of heart failure or a high risk of heart failure, a thiazide-like diuretic is recommended.

Clinical Guideline	Recommendations
	• 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. • If clinic blood pressure remains higher than 140/90 mm Hg after treatment with the optimal or best tolerated doses of an ACE inhibitor or an ARB plus a CCB plus a diuretic as resistant hypertension, and consider adding a fourth antihypertensive drug and/or seeking expert advice. • For resistant hypertension, consider further diuretic therapy with low dose spironolactone (25 mg daily) if the blood potassium level is less than 4.5 mmol/L. Consider a higher-dose thiazide-like diuretic if the blood potassium level is greater than 4.5 mmol/L.

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 mg 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.[15,33] Doses above 300 mg have not resulted in an increased blood pressure response but increased the rate of diarrhea.[33] Aliskiren was associated with an increase in plasma renin concentrations but a decrease in plasma renin activity.[33] In the Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints (ALTITUDE) trial, there was an increased incidence of non-fatal stroke, renal complications, hyperkalemia and hypotension in the aliskiren treatment arm when added to standard care in patients with type 2 diabetes and concomitant renal impairment. Aliskiren-containing products for use in combination with an angiotensin converting enzyme (ACE)-inhibitor or angiotensin II receptor blocker (ARB) will no longer be promoted by the manufacturer.[6] With these findings, the American Association of Clinical Endocrinologists recommends that physicians transition away from the use of aliskiren in combination with ACE inhibitor or ARBs in patients with diabetes and chronic kidney disease.[7]

Limited comparative studies of aliskiren with other antihypertensive agents, including the ACE inhibitors and ARBs have generally demonstrated similar efficacy when administered in comparable doses.[14-17,28] In general, the incidence of side effects was also comparable. One study reported greater efficacy and a lower incidence of cough with aliskiren compared to ramipril (2.1 vs 5.5%).[18] Schmieder et al compared monotherapy with aliskiren to monotherapy with hydrochlorothiazide and demonstrated significantly lower systolic and diastolic blood pressures and better overall response rates at weeks 6 and 12 with aliskiren, though the significant difference in systolic blood pressure was not maintained at week 52.[19] 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.[37] Overall, aliskiren appears to be well tolerated with clinical studies 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.[2-5] Four combination renin inhibitors are currently available, and none are available generically. Amturnide®, a combination of aliskiren, amlodipine and hydrochlorothiazide, is not indicated for initial treatment of hypertension.[4] Clinical studies 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.[22-29] Drummond et al compared the combination of daily aliskiren/amlodipine 150/5 mg to monotherapy with amlodipine 5 mg 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.[27] In a study of African American patients with hypertension, the combination of aliskiren/hydrochlorothiazide was not significantly more effective in regard to reducing systolic blood pressure compared to amlodipine monotherapy, after eight weeks of treatment.[32] Alternatively, in a trial that included patients with hypertension and type 2 diabetes mellitus, aliskiren/hydrochlorothiazide demonstrated a significant greater mean reduction in sitting systolic blood pressure compared to amlodipine alone.[29]

To date, there are no long-term trials evaluating the safety and efficacy of aliskiren or 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.[44-47] 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.[12] The completion of long-term trials with clinical 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.

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