Aliskiren for the Treatment of Hypertension: An Update

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Abstract: Hypertension can lead to significant morbidity and mortality, and requires lifestyle modifications with or without drug therapy to achieve target blood pressure control. Various classes of anti-hypertensive medications are available to healthcare providers. Choice of medications is based not only on efficacy but also tolerability and cost. Aliskiren is the first drug of a new class of agents known as renin inhibitors. It is approved by the U.S. Food and Drug Administration (FDA) as monotherapy or combination therapy with other antihypertensive agents to optimize blood pressure control. Its efficacy in blood pressure reduction is superior to placebo and comparable to angiotensin receptor blockers, hydrochlorothiazide, angiotensin-converting-enzyme inhibitors and atenolol. It also offers additional blood pressure reduction when used in combination of other agents. Recently, a study demonstrated its efficacy and safety in the elderly, and a study suggested its renoprotective effects in patient who were already taking losartan. More clinical studies are awaited to assess its potential for cardiovascular disease risk reduction. This paper reviews the pharmacology, efficacy and safety of aliskiren for the treatment of hypertension.

Keywords: systolic hypertension, cardiovascular disease, renin inhibitor

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Introduction
Hypertension affects more than sixty-five million adults in the United States, and is a common disease in the elderly. The prevalence of hypertension increases with age. The overall prevalence of hypertension is approximately 30%; however, the prevalence of hypertension in individuals over 60 years of age is approximately 65%. A prospective cohort study of participants from the Framingham Heart Study found that 9 out of 10 middle aged and older adults are likely to develop hypertension over their remaining lifetime.

Hypertension is usually defined as blood pressure greater than 140/90. Elderly individuals, however, often have isolated systolic hypertension which is defined as a systolic blood pressure of 160 mmHg or greater and a diastolic blood pressure of less than 90 mmHg. Studies have shown that treatment of isolated systolic hypertension in elderly individuals significantly reduces the incidence of stroke, cardiovascular events and death. In addition, the Hypertension in the Very Elderly Trial (HYVET) found that treatment of hypertension in individuals 80 years of age and older was beneficial in reduction of stroke, cardiovascular mortality, risk of heart failure and death from all causes.

While the prevalence of hypertension in the elderly has not declined significantly, the awareness, treatment, and control rates of hypertension in the over 60 age group have increased. However, the treatment of hypertension in the elderly population remains challenging. The current pharmacotherapy guideline recommends a stepwise approach to treatment of hypertension beginning with lifestyle modification to monotherapy or combination therapy. Often two or more medications with different mechanism of action are necessary to achieve blood pressure goals. Currently available antihypertensive agents include diuretics, aldosterone-receptor blockers, beta-blockers, alpha-blockers, combined alpha and beta-blockers, angiotensin-receptor blockers, angiotensin II receptor blockers (ARB’s), calcium channel antagonists, central alpha antagonists, and direct vasodilators.

Each agent carries tolerability issues which may limit its use based on the patient factors. Diuretics, ACE inhibitors and ARB’s may contribute to renal dysfunction and electrolyte disturbances. Beta-blockers and non-dihydropyridine calcium channel antagonists (verapamil, diltiazem) can be associated with bradycardia. Alpha blockers and direct vasodilators may exacerbate orthostatic hypotension and increase risk for falls in patients with abnormalities of balance and gait.

Choice of medications is based not only on efficacy but also tolerability and cost. Thiazide diuretics are generally felt to be the most appropriate first line drug in the treatment of elderly hypertension. However, the presence of urinary incontinence and development of electrolyte abnormalities (hypokalemia and hyponatremia) often lead to poor compliance and adverse side effects. Other factors make treatment of hypertension in the elderly oftentimes difficult. These factors include impairment of baroreceptor activity and decreased intravascular volume which predispose the elderly to orthostatic hypotension. Also, decreased renal and hepatic function in the elderly limit the use of some antihypertensive agents, such as beta blockers, ACE inhibitors, ARB’s. In addition, the presence of cognitive impairment makes the use of multiple antihypertensive medications problematic in that there is more likelihood of noncompliance and medication errors. Elderly patients are often on multiple drugs and they are prone to adverse side effects from medications which can also affect compliance and efficacy. Therefore, treatment of hypertension in the elderly must be highly individualized with the ultimate goal of normalizing blood pressure with minimal side effects or adverse reactions. A newer agent, aliskiren (Tekturna; Novartis, East Hanover, NJ) is the first drug of a new class of agents known as renin inhibitors, ARB’s. The U.S. Food and Drug Administration (FDA) approved aliskiren in March 2007 as monotherapy or combination therapy with other antihypertensive agents to optimize blood pressure control.

Pharmacology
The renin-angiotensin-aldosterone system (RAAS) has been a major target site for ACE inhibitors and ARBs. Renin is a protease enzyme secreted by the juxtaglomerular cells in the kidney in response to reduced blood volume and renal perfusion, or increased sympathetic central nervous system
activity. Renin cleaves angiotensinogen to form the inactive Ang I, which is converted to the active Ang II by ACE and non-ACE pathways. Ang II is a powerful vasoconstrictor and leads to the release of catecholamines and the mineralocorticoid aldosterone.\(^\text{10}\) Additionally, Ang II has been associated with other deleterious cardiovascular effects including inflammation, remodeling, hypertrophy, and thrombosis.\(^\text{11}\) Increased level of Ang II also inhibits the release of renin. As a result of this negative feedback mechanism, renin becomes the major determinant of RAAS activity and a main target for inhibiting Ang-II-related physiologic effects. Aliskiren is a nonpeptide, low-molecular-weight, orally active renin inhibitors designed through a combination of molecular modeling techniques and crystal structure elucidation.\(^\text{12}\) It binds with high specificity to the proteolytic active sites of renin.\(^\text{12}\) It has an extended half-life allowing once daily oral administration.

Aliskiren lowers blood pressure by inhibiting renin and therefore the circulating levels of Ang I and Ang II.\(^\text{9,10}\) Its mechanism of action leads to a reduced Ang II level, a compensatory rise in plasma renin concentration, a reduced functional plasma renin activity and a reduced urinary aldosterone excretion. In healthy normotensive volunteers, it does not change heart rate and has a duration of action of 48 hours.\(^\text{13,14}\)

**Clinical Trials**

A summary of early clinical trials of aliskiren for the treatment of hypertension can be found elsewhere.\(^\text{16}\) Overall, aliskiren was shown to be effective when compared to ARBs (losartan, irbesartan), when used in combination with ARBs (valsartan, irbesartan), a diuretic (hydrochlorothiazide) and an ACEI (ramipril). Recent clinical trials suggest the renoprotective effect of aliskiren in patients with hypertension, diabetes mellitus and nephropathy. Here we supplement the published review article with newer clinical data of aliskiren when compared or used in combination with ACE inhibitors or beta blockers.

**Aliskiren versus angiotensin II receptor blockers**

A review article describes randomized double-blind dose ranging clinical trials that compared aliskiren with ARBs (losartan and irbesartan) in patients with mild to moderate hypertension.\(^\text{16}\) In brief, Stanton et al.\(^\text{17}\) demonstrated that 4-week therapy of aliskiren 150 mg or 300 mg daily provided similar efficacy compared to losartan 100 mg daily with SBP reductions of 10–14 mmHg and DBP reductions of 2–8 mmHg. Most common adverse effects of aliskiren were fatigue, weakness, gastrointestinal complaints and headache. Rates of adverse effects were comparable (11% to 35% for aliskiren vs. 32% losartan) although reversible chest tightness/cardiac ischemic event and hypotension occurred in the aliskiren group only. In another trial, Gradman et al.\(^\text{18}\) showed a dose-related antihypertensive effect of aliskiren for up to 300 mg daily. Aliskiren further reduced SBP by 6 to 10 mmHg and DBP by 3 to 5 mmHg compared to placebo (all p values significant). It further reduced DBP by about 3 mmHg when compared to irbesartan 150 mg daily (p \(\text{<} 0.05\)). More patients receiving higher doses of aliskiren achieved blood pressure control (<140/90 mmHg) compared to those receiving placebo and irbesartan (38%–50% aliskiren, 34% irbesartan, 21% placebo; p < 0.05 for both comparisons). The most common adverse effects were nervous system symptoms (6.3%–10.0% aliskiren, 9.2% placebo, and 6.7% irbesartan) and gastrointestinal symptoms (3.9%–9.2% aliskiren, vs. 3.8% placebo, and 6.7% irbesartan).

In a newer multicenter, randomized, double-blind, placebo-controlled, parallel-group study, Nussberger

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**Pharmacokinetics/Dynamics**

Aliskiren has a very low bioavailability (~2.5%), and reaches the peak plasma concentration within 1 to 6 hours.\(^\text{9,12}\) High fat meals reduce the drug exposure and peak plasma concentration by 71% and 85%, respectively.\(^\text{9}\) Diminished drug exposure was also noted in the elderly. It has a small volume of distribution (<2 L/kg) and a half-life of approximately 24 hours with a steady-state drug level achieved in 5–8 days.\(^\text{9,13}\) It has modest water solubility with moderate protein binding (50%).\(^\text{22}\) It is metabolized by liver cytochrome P450 enzyme 3A4.\(^\text{9}\) More than 90% of aliskiren is eliminated unchanged in the feces, <2% is eliminated as oxidized metabolites, and <1% is eliminated in the urine.\(^\text{12}\) Diabetic patients have a higher drug exposure due to a slower drug clearance (205 vs. 234 L/h) and a longer elimination half-life (44 vs. 40 hours).\(^\text{15}\)
et al19 studied 569 adult patients with mild-to-moderate hypertension (DBP 95–110 mmHg). Patients received either aliskiren (150, 300 or 600 mg), irbesartan 150 mg or placebo once daily for 8 weeks. Results showed that both aliskiren and irbesartan significantly reduced SBP by 11–16 mmHg from baseline (p < 0.001 vs. placebo).

Aliskiren combined with angiotensin II receptor blockers

In a randomized, double-blind, single dose crossover trial, Azizi et al20 assessed the effects of an aliskiren-valsartan combination in twelve healthy, mildly sodium-depleted, normotensive male volunteers (age 18 to 35). The reductions in mean arterial pressure at 4 hours post-dose were 6.6, 4.9 and 7.4 mmHg for valsartan 160 mg, aliskiren 300 mg and aliskiren/valsartan 150/80 mg, respectively. However, the benefits were reversed at 48 hours (increases of 2.6 and 0.8 mmHg, for aliskiren and aliskiren/valsartan, respectively, and a reduction of 0.9 mmHg for valsartan). This study suggests that aliskiren is inferior to valsartan despite the limitations of its study design. Nevertheless, a larger multicenter randomized trial had a different result. Pool et al21 randomized 1123 patients to receive various doses of aliskiren, valsartan, aliskiren/valsartan combination, valsartan/hydrochlorothiazide (HCTZ) combination, or placebo daily. At week 8, placebo reduced blood pressure by 10.0/8.6 mmHg; aliskiren groups reduced SBP by 12.1 to 15.0 mmHg and DBP by 10.3 to 12.3 mmHg; valsartan groups reduced SBP by 11.2 to 16.5 mmHg and DBP by 10.5 to 11.3 mmHg. Overall, all three aliskiren-valsartan combinations significantly lowered blood pressure compared with placebo. Aliskiren-valsartan 150/160 and 300/320 mg has similar efficacy compared with valsartan/hydrochlorothiazide 160/12.5 mg. The most commonly adverse effects were headache (5.7%), fatigue (2.8%), back pain (1.8%), and diarrhea (1.6%). Eight patients (0.7%) experienced serious adverse events (details not reported). One patient receiving aliskiren experienced a worsening of renal function (serum creatinine >2 mg/dL). Five cases of hyperkalemia were distributed equally among treatment groups. Limitations of this study include a large placebo response (SBP reduction 8.6 mmHg, DBP reduction 10 mmHg, and 48% response rate with placebo) and lack of power to compare the combination treatments to their component monotherapies.

In another 8-week randomized, double-blind, placebo-controlled, dose-escalation study, Oparil et al compared the effect of aliskiren or valsartan monotherapy to aliskiren with valsartan combination therapy.22 A total of 1797 adult patients with essential hypertension (mean sitting diastolic blood pressure of 95 to <110 mmHg) were randomized to received aliskiren 150 mg, valsartan 160 mg, the combination of aliskiren 150 mg and valsartan 160 mg, or placebo daily for 4 weeks with dose titration for another 4 weeks. At the week 8 endpoint, monotherapy with aliskiren or valsartan provided significantly greater reductions in SBP and DBP than placebo (all p < 0.0001). In addition, combination therapy of aliskiren and valsartan reduced SBP and DBP by 17.2 mmHg and 12.2 mmHg from baseline, which was significantly more than aliskiren monotherapy (13 mmHg and 9 mmHg; p < 0.0001) or valsartan (12.8 mmHg and 9.7 mmHg; p < 0.0001), or placebo (4.6 mmHg and 4.1 mmHg; p < 0.0001). Adverse events occurred in similar rates in placebo and all treatment groups. The most common adverse events in treatment groups were headache (3%–5%), nasopharyngitis (3%–4%), and dizziness (2%). Occurrences of hyperkalemia were 2% in monotherapy groups and 4% in combination group (vs. 3% in placebo group).

Aliskiren combined with a diuretic

In a multicenter, randomized, double-blind, 8 week trial, Villamil et al23 compared aliskiren, HCTZ, aliskiren/HCTZ combination and placebo in 2776 hypertensive patients (DBP 95–109 mmHg). Compared to placebo, aliskiren 300 mg provided an additional blood pressure reduction of 8.2/3.4 mmHg (p < 0.0001). Aliskiren/HCTZ 300/25 mg provided an additional reduction of 13.7/7.4 mmHg (p < 0.0001 vs. placebo; p < 0.05 vs. each component monotherapies). Aliskiren monotherapy resulted in a similar rate of adverse effects, yet the rate increased when combining with HCTZ (HCTZ up to 11%; aliskiren up to 9.8%; aliskiren/HCTZ up to 16.6%; and placebo 8.8%). Aliskiren was associated with lower incidence of hypokalemia compared to HCTZ (0.6%–5.2% vs. 0%–1.5% aliskiren; 0.7%–3.4% aliskiren/HCTZ; and
1.3% placebo). Of note, discontinuation rates due to adverse effects occurred more frequently in aliskiren 300 mg group (4.4% vs. 3.6% placebo).

Aliskiren versus ACEI

In a 26-week, randomized, double-blind, multicenter study that was published in 2008, Andersen et al compared the efficacy, safety and tolerability of aliskiren and ramipril-based therapy for the treatment of patients with mild-to-moderate hypertension (DBP ≥ 90 mmHg and <110 mmHg). Aliskiren-based therapy (i.e. aliskiren alone or combined with HCTZ) lowered SBP and DBP by 18 mmHg and 13 mmHg from baseline, respectively. Ramipril-based therapy reduced SBP and DBP by 15 mmHg and 12 mmHg, respectively. The mean reductions in SBP and DBP were significantly greater with aliskiren-based therapy than with ramipril-based therapy (p = 0.0036 and p = 0.025, respectively) although the small absolute reductions are unlikely to be clinically significant. The majority of adverse events reported were mild or moderate in intensity and transient. Cough was reported more frequently with ramipril (9.5%) than aliskiren (4.1%). Headache was more common with aliskiren (11.2% vs. 8.3%).

Aliskiren combined with beta blocker

Rainer et al compared the efficacy, safety and tolerability of aliskiren with atenolol in patients with hypertension in a randomized double-blind trial. A total of 694 patients were randomized to receive aliskiren 150 mg (n = 231), atenolol 50 mg (n = 231), or the combination (n = 232) for 12 weeks. The reductions in SBP/DBP from baseline were 14.3/11.3, 14.3/13.7 and 17.3/14.1 mmHg for aliskiren, atenolol, and the combination, respectively. Rates of BP control (<140/90 mmHg) at week 12 endpoint were higher with the aliskiren 300 mg/atenolol 100 mg combination (51.3%) than with either aliskiren (36.1%, p < 0.001) or atenolol alone (42.2%, p = 0.009). There was no significant difference in blood pressure control rates in the monotherapy arms with either aliskiren or atenolol (p = 0.388). Most common adverse events were headache (aliskiren 4.3%, atenolol 6.1% vs. combination 5.6%), nasopharyngitis (aliskiren 3.5%, atenolol 6.5% vs. combination 1.3%) and hyperkalemia (aliskiren 5%, atenolol 8.8% vs. combination 7.8%). Bradycardia was reported in 2.2% in atenolol group (vs. 0% in aliskiren and 1.3% in combination groups).

Indication/Dosage

Aliskiren is approved by the FDA as monotherapy or combination therapy for hypertension. The recommended starting dose is 150 mg once daily, and may be increased to 300 mg daily to target blood pressure control. No dosage adjustment is necessary for advanced aged or renal/hepatic insufficiency. The efficacy should be seen within 2 weeks of therapy.

Contraindications/Precautions

Hyperkalemia can occur when used in combination with an ACE inhibitor or ARB. Hypotension may occur, especially when used in combination with other antihypertensive agents. Use of aliskiren should be cautioned in patients with renal dysfunction (serum creatinine ≥1.7 mg/dL for women; ≥2.0 mg/dL for men and/or estimated glomerular filtration rate <30 mL/min), a history of dialysis, nephrotic
syndrome, or renovascular hypertension. Aliskiren is contraindicated during pregnancy and in patients who experience angioedema with its use.

**Adverse Effects**
The safety of aliskiren has been evaluated in approximately 6,460 patients for up to 1 year. Rate of adverse events that lead to drug discontinuation were similar to that of placebo (2.2% vs. 3.5% placebo). Angioedema with or without respiratory symptoms occurred in 0.06% of patients receiving aliskiren. Edema of the face, hands, or whole body (26 cases) and diarrhea (2.3% vs. 1.2% placebo) have been reported. Other gastrointestinal side effects included abdominal pain, dyspepsia, and gastroesophageal reflux; all of which are typically mild in severity. Cough has been reported (1.1% vs. 0.6% placebo) in clinical studies, but it occurred less frequently than in the ACE inhibitor groups. Worsening of renal function has been observed (7% vs. 6% placebo) as has anemia (0.1% aliskiren all doses, 0.3% aliskiren 600 mg, vs. 0% placebo). Other adverse effects reported in clinical trials include rash (1% vs. 0.3% placebo), hyperkalemia (0.9% vs. 0.6% placebo, 5.5% ACEI), elevated uric acid (0.4% vs. 0.1% placebo), gout (0.2% vs. 0.1%), and renal stones (0.2% vs. 0%). Two cases of tonic-clonic seizures with loss of consciousness were reported in clinical trials. Elevation of creatine kinase has led to one case of subclinical rhabdomyolysis and another case of myositis.

**Drug Interactions**
Aliskiren is metabolized by liver enzyme cytochrome P450 3A4. Co-administration of other 3A4 substrates, such as atorvastatin and ketoconazole, can significantly increase its plasma level due to competitive enzyme inhibition. Studies report no drug interactions with lovastatin, atenolol, celecoxib, cimetidine or warfarin. Aliskiren decreases the plasma drug concentration of furosemide which may require a dose increase. In addition, risk for hypotension should be monitored when aliskiren is used in combination with other antihypertensives. High-fat meals may reduce drug absorption of aliskiren, but the clinical significance remain unclear.

**Use in Special Population**
Use of aliskiren should be avoided during pregnancy (category-C during the 1st trimester and category-D during the 2nd and 3rd trimesters). It is unknown if aliskiren is excreted in human milk. Its safety and efficacy have not been evaluated in pediatric patients. The elderly subjects in clinical studies experienced similar effects compared to the younger population. No dosage adjustment has been established based on gender, age, race or hepatic/renal impairment. Nevertheless, use of aliskiren should be cautioned in patients with severe renal impairment. Diabetic patients have a higher drug exposure due to a slower drug clearance (205 vs. 234 L/h) and a longer elimination half-life (44 vs. 40 hours). Aliskiren has been evaluated for its renal protective effect in patients with diabetes. In a multinational, randomized, double-blind study, Hans-Henrik et al evaluated 599 patients with hypertension, type 2 diabetes and nephropathy. Aliskiren or placebo was added to an ARB, losartan for additional 6 months. Aliskiren reduced the mean urinary albumin-to-creatinine ratio by 20% (p < 0.001), A reduction of >50% in albuminuria was seen in 24.7% of the patients who received aliskiren, as compared with 12.5% of the patients who received placebo (p < 0.001). This study suggested that aliskiren have renoprotective effects that are independent of it blood pressure lowering effect. However, it comparative effect in relative to other known renoprotective agents, such as ACE inhibitors or ARBs, remain unknown.
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contraindications to study medications, were excluded. Because this study involved 24-hour ambulatory blood pressure monitoring (ABPM), night-shift workers or those who had an arm circumference outside the limits of the ABPM cuff were also excluded. A total of 598 patients entered the single-blind placebo run-in period, of whom 355 were randomized to treatment with aliskiren 75 mg (n = 75), aliskiren 150 mg (n = 84), aliskiren 300 mg (n = 94), or lisinopril 10 mg (n = 86). All three aliskiren doses produced significant blood pressure reduction from baseline (p < 0.001) with no statistically significant differences observed between the groups (SBP 2 mmHg and DBP 1 mmHg). Significant blood pressure reductions were observed with lisinopril (p < 0.0001 vs. baseline). A significantly greater proportion of patients receiving aliskiren 300 mg achieved BP control compared with those receiving aliskiren 75 mg (p = 0.033). Most common adverse effects were dizziness (aliskiren 3%–6%; lisinopril 2.3%), headache (aliskiren 2.4%–3.3%; lisinopril 5.8%), diarrhea (aliskiren 3.6%–4.3%; lisinopril 1.2%), nasopharyngitis (aliskiren 1.1%–2.4%; lisinopril 2.3%). Hyperkalemia was reported in 1.1 to 4.4% patients with aliskiren vs. 0% in lisinopril group.

Availability and Cost
Aliskiren is available as unscored tablets (150 mg and 300 mg). It is more costly than generically available antihypertensives. The retail prices for a one-month supply with 150 mg once-daily and 300 mg once-daily are approximately $70 and $90, respectively.33

Conclusions
Aliskiren is the first antihypertensive in a novel drug class of direct renin inhibitors. Studies to date demonstrate its efficacy for blood pressure control with comparable tolerability to other available agents. However, studies in the geriatric population are limited.34 Studies are underway to assess the role of aliskiren in cardiovascular risk reduction,34 left ventricular hypertrophy,35 and diabetes.36 However, to date, there are no published outcome studies about aliskiren use or data for use in heart failure, a complication of hypertension prevalent in the elderly population. Although other agents acting on the renin system, ACE inhibitors and ARBs, have indications besides hypertension, such as congestive heart failure or nephropathy, Aliskiren does not have those indications. Long term studies are needed to determine if aliskiren can lead to similar organ protective benefits. Overall, aliskiren appears to have a role as an anti-hypertensive agent for adults with effective blood pressure effects with low rates of hyperkalemia. Because it is more expensive than generic or older antihypertensive agents, it should be considered as an alternative in patients who have contraindications or tolerability issues to existing treatment options. Until further data is available, caution may be warranted for use of aliskiren in patients with complicated hypertension. In summary, direct renin inhibitors are an exciting new class of antihypertensive medication with potential for greater impact with additional indications. Ongoing and future research will demonstrate whether aliskiren is beneficial for renal or cardiac risk reduction.

Disclosure
The authors report no conflicts of interest.

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