The Efficacy of Aliskiren, a Direct Renin Inhibitor, in the Treatment of Hypertension

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Aliskiren is a potent, highly specific renin inhibitor with better oral bioavailability than earlier renin inhibitors and a long plasma half-life that makes it suitable for once-daily dosing. The efficacy and safety of aliskiren in treating hypertension has been studied in clinical trials both as monotherapy, comparing it with existing antihypertensive therapies, and in combination with other antihypertensive agents, including the diuretic hydrochlorothiazide, the angiotensin-converting enzyme inhibitor ramipril, and the calcium channel blocker amlodipine. From the extensive database acquired to date, it is clear that aliskiren is an effective antihypertensive agent, with once-daily administration resulting in dose-dependent systolic and diastolic blood pressure reductions. Combinations with existing antihypertensives are producing promising additional blood pressure–lowering effects.

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Key words: Aliskiren • Renin inhibitors • Hypertension • Antihypertensives

Because renin catalyzes the rate-limiting step in the production of the vasoconstrictor peptide angiotensin II, it has long been postulated that direct renin inhibition would constitute the preferred pharmacologic approach to reducing blood pressure (BP) by suppressing the renin–angiotensin–aldosterone system (RAS).[1,2] Over the past 20 years, a number of renin inhibitors have been synthesized and studied in experimental animals and in humans, and several of these agents have proven to be clinically effective after parenteral administration. The large molecular size and lipophilicity of these compounds, however, results in poor intestinal absorption and considerable hepatic first-pass

metabolism, significantly limiting their oral bioavailability. Crystal structure analysis of renin-inhibitor complexes combined with computational methods were later used to design a novel class of low-molecular-weight, nonpeptide renin inhibitors, of which aliskiren is the most clinically advanced.[1-6]

Aliskiren is an extremely potent inhibitor (IC_{50} = 0.6 nmol/L) of human renin. It is highly specific for renin and has a more than 10,000-fold lower affinity for related human aspartic peptidases, and thus is unlikely to produce untoward side effects through interaction with other enzymes. The physicochemical properties of aliskiren, including its high water solubility and low lipophilicity, render it more resistant to biodegradation by peptidases in the gastrointestinal tract, blood, and liver. As a result, aliskiren exhibits improved oral bioavailability (approximately 2.6%) compared with earlier renin inhibitors. Yet another favorable pharmacokinetic property of aliskiren is its long plasma half-life ($t_{1/2}$ = 40 hours), making it suitable for once-daily administration.[2,3,6,7]

Aliskiren has now been studied, both as monotherapy and in combination with other antihypertensive agents, in clinical trials involving more than 7000 adult patients. Many of the critical questions relating to its suitability as an antihypertensive agent have been addressed, and additional studies are ongoing. The results of completed trials are summarized in this review.[8]

Pharmacokinetics of Orally Administered Aliskiren

The single- and multiple-dose oral pharmacokinetics of aliskiren have been investigated over a wide range of doses (40–1800 mg) in healthy subjects. Maximum plasma concentrations occur between 2 and 4 hours after oral administration. The hepatic extraction ratio is approximately 12%, indicating only minor involvement of first-pass metabolism in drug elimination. The majority of a single oral dose of aliskiren is excreted in the feces as unchanged drug. In healthy volunteers, urinary excretion of aliskiren accounts for only 0.1% to 1.1% of the administered dose at steady state. With multiple dosing, the terminal half-life of aliskiren is approximately 25 to 30 hours. In vitro inhibition data indicate that drug interactions with agents that are metabolically cleared by cytochrome P450 enzymes are unlikely.[3,6,7,9,10]

Aliskiren Monotherapy for Treating Hypertension

Five placebo-controlled clinical trials have evaluated the efficacy and safety of aliskiren monotherapy at doses of 75 to 600 mg administered once daily.[7,8,11,12] The subjects in these trials all had mild-to-moderate essential hypertension, defined as a seated diastolic BP between 95 and 110 mm Hg. In these studies, a 2- to 4-week single-blind placebo phase was followed by a double-blind treatment period that ranged from 4 to 8 weeks. The primary endpoint of each study was the change from baseline in mean sitting diastolic BP (msDBP). Secondary endpoints included change from baseline in mean sitting systolic BP (msSBP), responder rates (defined as percentage of patients achieving msDBP < 90 mm Hg and/or a 10 mm Hg reduction from baseline), as well as safety and tolerability. To assess for rebound hypertension, several of the trials included a monitored withdrawal phase.

The largest of the monotherapy studies included 672 male and female patients, with a mean age of 53 years. Aliskiren at doses of 150, 300, or 600 mg taken once daily was compared with placebo over an 8-week blinded treatment period. BP was monitored for an additional 2 weeks after discontinuation of study medication to assess for rebound hypertension. Dose-dependent BP reduction was observed across the range of administered aliskiren doses. The reduction in msDBP was 4.9 mm Hg for placebo and 10.3, 11.1, and 12.5 mm Hg for aliskiren doses of 150, 300, and 600 mg, respectively ($P < .0001$ vs placebo). Mean sitting systolic BP was reduced by 3.8 mm Hg in the placebo arm and by 13.0, 14.7, and 15.8 mm Hg at aliskiren doses of 150, 300, and 600 mg, respectively ($P < .05$ for aliskiren 600 mg vs. aliskiren 150 mg).[11]

Dose-dependent blood pressure reduction was observed across the range of administered aliskiren doses.

BP-lowering effects were observed early in the treatment phase, with most of the BP reduction achieved by week 2. Maximum effects of the 150- and 300-mg doses were reached by week 4 and sustained for the remainder of the 8-week blinded treatment period. Follow-up BP measurements during the washout period showed no evidence of a rebound effect on withdrawal of aliskiren. Interestingly, the antihypertensive effect of all doses of aliskiren persisted to some extent after treatment was discontinued. Both msSBP and msDBP rose during the withdrawal period but had not returned to placebo levels 2 weeks after aliskiren withdrawal.[11]

In this study, an important secondary endpoint was the ability of aliskiren to sustain its antihypertensive effect throughout the 24-hour dosing

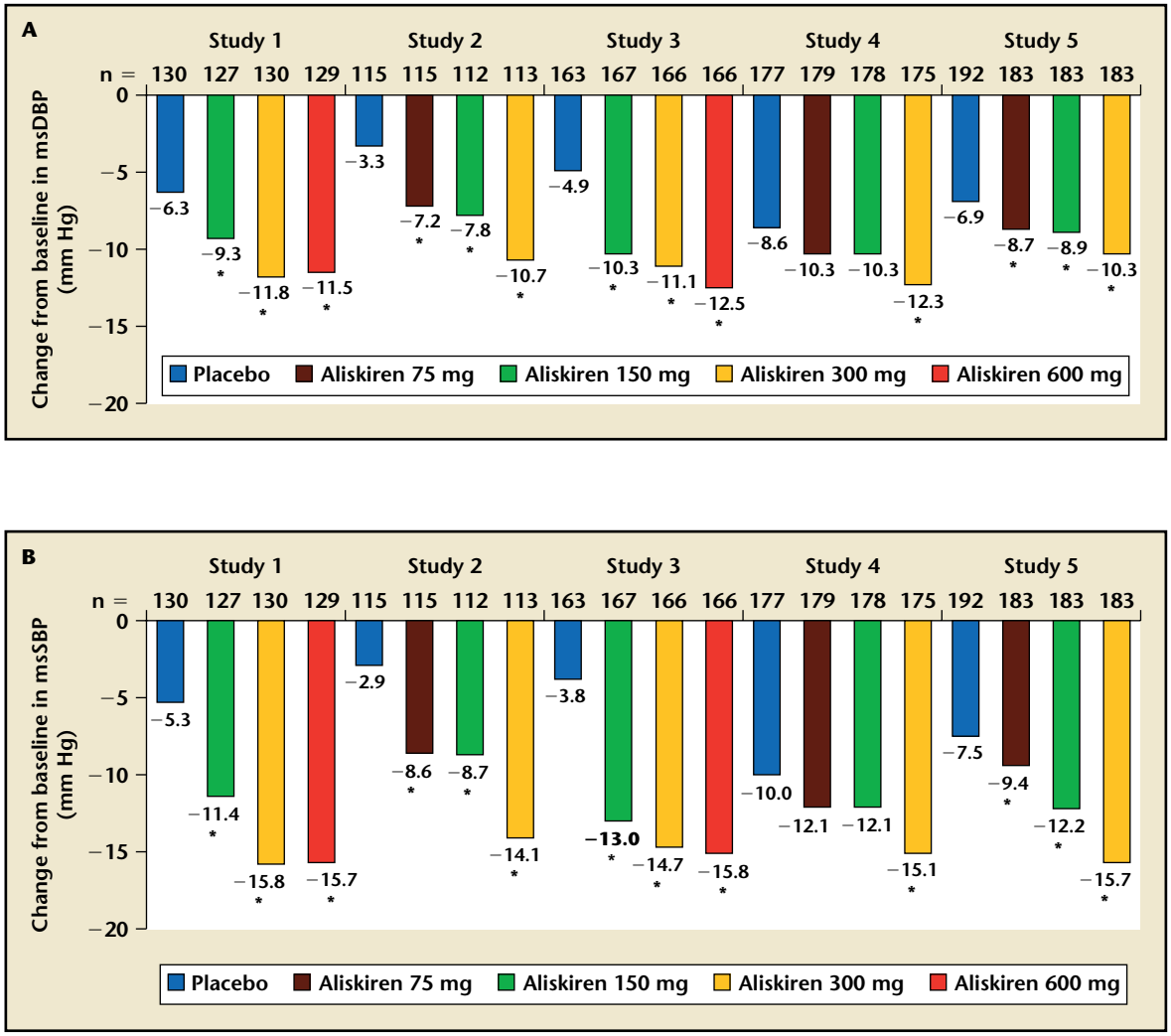


Figure 1. *Pooled analysis of data from 5 randomized, double-blind, multicenter clinical trials of aliskiren.* **(A)** *Effects on mean sitting diastolic blood pressure (msDBP). Aliskiren monotherapy lowers msDBP compared with placebo.* **(B)** *Effects on mean sitting systolic blood pressure (msSBP). Aliskiren monotherapy lowers msSBP compared with placebo.* *P $<$ .05 *vs placebo. HCTZ, hydrochlorothiazide. Data from Gradman et al,*[7] *Oh et al,*[11] *Villamil et al,*[12] *Kushiro et al,*[20] *and Pool et al.*[21]

interval, as measured by 24-hour ambulatory BP monitoring. Aliskiren at doses of 150, 300, and 600 mg once daily was statistically superior to placebo in reducing mean ambulatory systolic BP and diastolic BP over the 24-hour dosing interval ($P < .0001$). There was no apparent loss of effect at trough, with a trough-to-peak ratio of 64% for the 150-mg dose and 98% for the 300-mg dose of aliskiren.[11]

Overall, the results of all 5 monotherapy studies were consistent with respect to the magnitude of achieved BP reduction (Figure 1). In the 1 other study evaluating the 600-mg dose, the peak of the dose–response relationship for BP reduction seemed to be reached at 300 mg, and no additional BP reduction was observed when the 600-mg dose was administered.[7] Responder rates for the 300-mg dose ranged from 63% to 68%. No significant differences in the magnitude of BP reduction were observed when men and women were compared, or when patients aged 65 years or more were compared with younger individuals.[8]

As shown in Table 1, aliskiren exhibited placebo-like tolerability at doses up to 300 mg once daily. The total number of reported adverse events and the rate of discontinuation due to adverse events were similar to those for placebo. The occurrence of headache was statistically reduced at aliskiren doses of 150 and

Table 1
Aliskiren Demonstrated Placebo-Like Tolerability at Doses up to 300 mg Once Daily

	Placebo (n = 781)	Aliskiren 75 mg (n = 478)	Aliskiren 150 mg (n = 774)	Aliskiren 300 mg (n = 768)	Aliskiren 600 mg (n = 296)	All Aliskiren (n = 2316)
Any SAE	5 (0.6)	3 (0.6)	3 (0.4)	4 (0.5)	1 (0.3)	11 (0.5)
Any AE	314 (40.2)	193 (40.4)	290 (37.5)	309 (40.2)	130 (43.9)	922 (39.8)
Discontinuations due to AE	27 (3.5)	8 (1.7)	12 (1.6)	20 (2.6)	5 (1.7)	45 (1.9)
AE reported by ≥ 2% of patients for aliskiren monotherapy overall						
Headache	68 (8.7)	31 (6.5)	42 (5.4)*	44 (5.7)*	15 (5.1)	132 (5.7)†
Nasopharyngitis	45 (5.8)	34 (7.1)	33 (4.3)	29 (3.8)	5 (1.7)†	101 (4.4)
Diarrhea	9 (1.2)	6 (1.3)	9 (1.2)	18 (2.3)	28 (9.5)‡	61 (2.6)*

Data are presented as n (%). SAE, serious adverse event; AE, adverse event.
*$P < .05$; †$P < .01$; ‡$P < .0001$ vs placebo.
Data from Weir et al.[8]

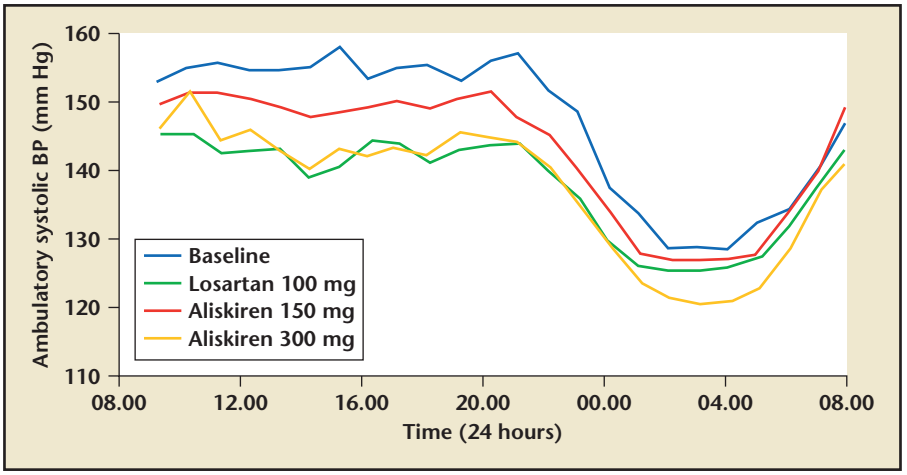
300 mg. At the 600-mg dose, an increased incidence of diarrhea (9.5%) compared with placebo (1.2%) was observed.[8]

Comparison With Other Antihypertensive Agents

Two dose-ranging trials in hypertensive patients compared the efficacy and safety of various doses of aliskiren with angiotensin receptor blockers (ARBs).[7,13] In a 4-week study, aliskiren in doses of 37.5, 75, 150, or 300 mg once daily was compared with losartan 100 mg once daily. Eligible patients had off-treatment average daytime ambulatory systolic BP ≥ 140 mm Hg. Mean reduction in daytime systolic BP was 0.4, 5.3, 8.0, and 11.0 mm Hg with aliskiren doses of 37.5, 75, 150, and 300 mg, respectively. Heart rate was unchanged with aliskiren. The change in daytime systolic BP with 100 mg of losartan was 10.9 mm Hg, similar to that observed with 300 mg of aliskiren. Both aliskiren and losartan provided reduction in systolic BP over a 24-hour monitoring period (Figure 2). The adverse event rates with aliskiren and losartan were similar.[13]

In a larger phase II study, Gradman and colleagues[7] randomized 652 patients with mild-to-moderate hypertension (mean DBP ≥ 95 mm Hg and < 110 mm Hg) for treatment with either once-daily oral doses of aliskiren (150, 300, or 600 mg), irbesartan (150 mg), or placebo. At the end of the 8-week treatment period, aliskiren doses of 150, 300, and 600 mg reduced trough msSBP by 10.8, 15.5, and 15.6 mm Hg, respectively, compared with a reduction of 5.1 mm Hg in the placebo group ($P < .001$) and 12.5 mm Hg with irbesartan. Aliskiren 300 mg and 600 mg lowered msDBP significantly more than irbesartan 150 mg ($P < .05$). The primary outcome variable in this study was change from baseline in trough msDBP. At the end of the 8-week treatment period, aliskiren doses of 150, 300, and 600 mg reduced trough msDBP by 9.3, 11.8, and 11.5 mm Hg, respectively, compared with a reduction of 6.3 mm Hg in the placebo

Figure 2. *Effects of placebo, losartan, and aliskiren on blood pressure (BP) over a 24-hour period. Adapted with permission from Stanton et al.[13]*



group and 8.9 mm Hg in patients receiving irbesartan. The percentage of patients who achieved BP control (defined as BP < 140/90 mm Hg) was similar with aliskiren 150 mg (37.8%) and irbesartan 150 mg (33.8%). Responder rates with the 300-mg (50.0%) and 600-mg (45.7%) doses of aliskiren were statistically greater than those achieved with irbesartan 150 mg. The incidence of adverse events and study discontinuations as a result of adverse effects during aliskiren treatment was low (< 4%) and similar to the results obtained in patients treated with placebo or irbesartan.

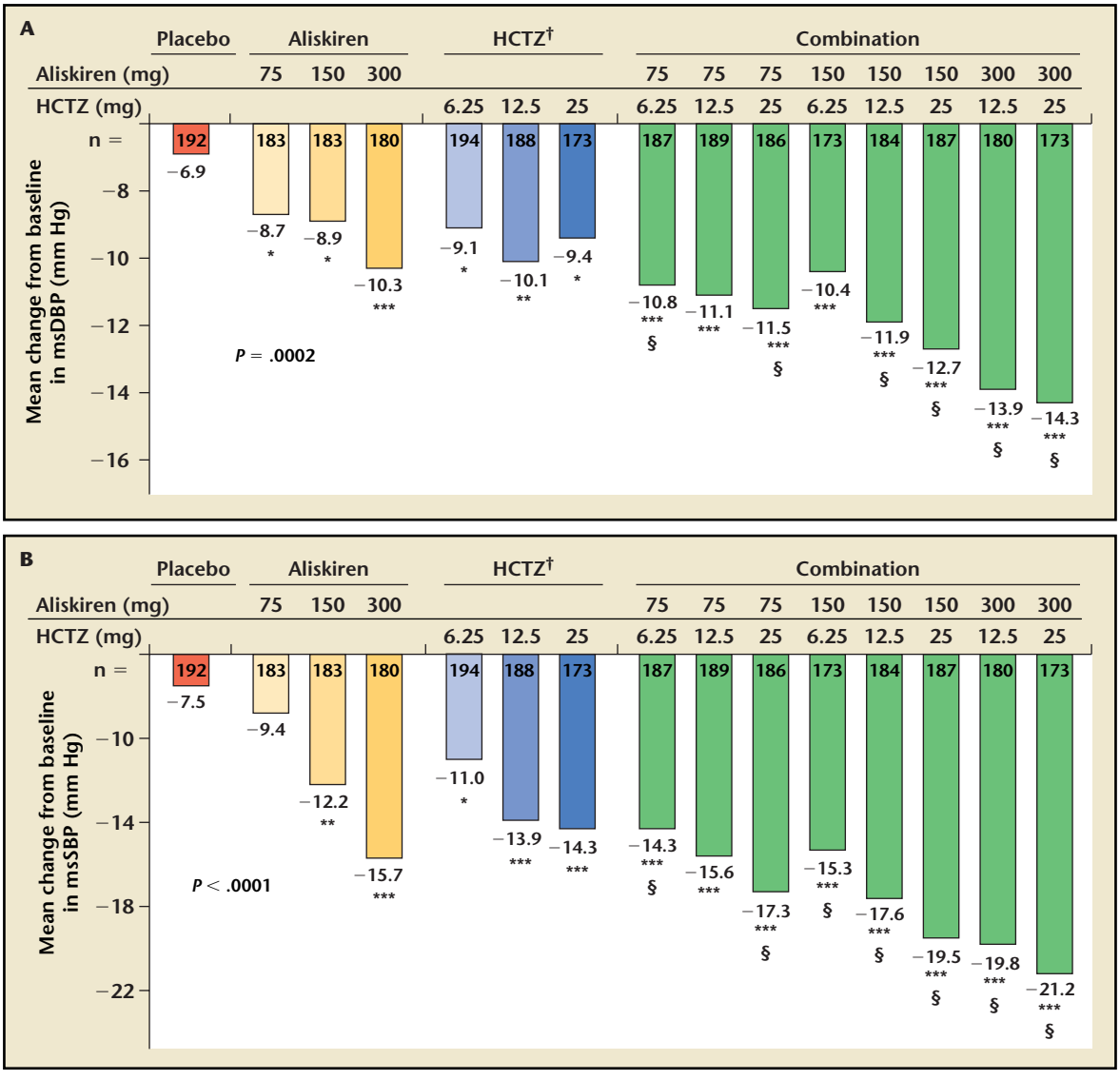
Aliskiren has also demonstrated equivalent antihypertensive efficacy compared with usual doses of the diuretic hydrochlorothiazide (12.5 and 25 mg) and the angiotensin-converting enzyme (ACE) inhibitor ramipril (10 mg).[12,14-16] These data, derived from studies designed to evaluate the effects of aliskiren in combination with other antihypertensive agents, are discussed below.

Combination Therapy

Aliskiren With a Low-Dose Diuretic

A study comparing aliskiren with hydrochlorothiazide (HCTZ) and evaluating the effects of combination therapy with both of these agents is the largest clinical trial conducted with aliskiren to date. In this factorial

Figure 3. *Effects of aliskiren, hydrochlorothiazide (HCTZ), and various aliskiren/HCTZ combination doses on office-measured blood pressure (BP).* **(A)** *Effects on mean sitting diastolic blood pressure (msDBP). Aliskiren provides additional diastolic BP lowering when combined with HCTZ.* **(B)** *Effects on mean sitting systolic blood pressure (msSBP). Aliskiren provides additional systolic BP lowering when combined with HCTZ. †Overall significance of HCTZ effect not tested. Pairwise comparisons: *P < .05, **P < .001, ***P < .0001 vs placebo; §P < .05 vs each component monotherapy. Reprinted with permission from Villamil et al.[12]*



design study, 2776 male and female patients with mild-to-moderate hypertension were randomized to receive 8 weeks of treatment with placebo, aliskiren (75, 150, 300 mg), HCTZ (6.25, 12.5, 25 mg), or various combination doses of aliskiren and HCTZ. The overall results are shown in Figure 3. Consistent with previous studies, aliskiren monotherapy resulted in a dose-dependent decrease in msSBP and msDBP. The mean BP reduction was 12.2/8.9 mm Hg with aliskiren at a dose of 150 mg once daily and 15.7/10.3 mm Hg with 300 mg once daily. Monotherapy with HCTZ at doses of 12.5 and 25 mg produced mean BP reductions of 13.9/10.1 and 14.3/9.4 mm Hg, respectively.[12]

Both aliskiren and hydrochlorothiazide made significant contributions to the reduction in mean sitting systolic BP and mean sitting diastolic BP, and additional reductions in BP were obtained with the combination.

When the effects of combined therapy were evaluated, 7 of the 8 dose combinations studied resulted in superior BP reduction compared with the corresponding component monotherapies ($P < .05$). Robust BP reduction (−21.2/14.3 mm Hg) was achieved with the highest combined dose of aliskiren/HCTZ, 300 mg/25 mg. The combination of the starting dose of aliskiren, 150 mg, with 12.5 mg of HCTZ also resulted in highly significant BP reduction (–17.6/11.9 mm Hg). With these 2 doses, the combined efficacy was statistically superior to monotherapy. Both aliskiren and HCTZ made significant contributions to the reduction in msSBP and msDBP, and additional BP reductions were seen with the combination.[12]

An additional effect of combination therapy was reduced incidence of hypokalemia (defined as serum $K^+ < 3.5$ mmol/L) in patients receiving HCTZ. With the addition of aliskiren, the frequency of hypokalemia dropped to 0.7% in patients receiving HCTZ 12.5 mg and 2.0% in those receiving HCTZ 25 mg.[12]

Dual RAS Blockade With Aliskiren and an ACE Inhibitor

The antihypertensive efficacy of dual RAS blockade with aliskiren in combination with the ACE inhibitor ramipril was compared with either agent alone in 837 patients with type 1 or type 2 diabetes and msDBP between 95 and 110 mm Hg. In this double-blind study, patients were randomized to receive monotherapy with aliskiren 150 mg, ramipril 5 mg, or the combination of aliskiren 150 mg and ramipril 5 mg. After 4 weeks of therapy, all patients were force-titrated to higher doses of their assigned treatments (aliskiren 300 mg, ramipril 10 mg, or aliskiren 300 mg/ramipril 10 mg, once daily) for an additional 4 weeks. The primary endpoint of the study was the change in msDBP from baseline.[14,17,18]

When monotherapy with 300 mg of aliskiren was compared with 10 mg of ramipril once daily, the reductions in diastolic BP were equivalent. The mean systolic BP reduction was greater with aliskiren (−14.7 mm Hg) than with ramipril (−12.0 mm Hg).[14,17,18]

Combination therapy with aliskiren and ramipril reduced mean sitting diastolic BP by 12.8 mm Hg, a significantly greater reduction than either monotherapy (aliskiren, –11.3 mm Hg; ramipril, –10.7 mm Hg).

Combination therapy with aliskiren and ramipril reduced msDBP by 12.8 mm Hg, a significantly greater reduction than either monotherapy (aliskiren, −11.3 mm Hg; ramipril, −10.7 mm Hg). Reduction in msSBP was also greater with the aliskiren/ramipril combination (−16.6 mm Hg; $P < .05$) than with ramipril monotherapy (−12.0 mm Hg). Although a greater systolic BP reduction was achieved with aliskiren/ramipril than with aliskiren alone, this effect did not reach statistical significance. Responder rates (percentage of patients with msDBP < 90 mm Hg or reduced by ≥ 10 mm Hg) were significantly greater with aliskiren/ramipril combination therapy (74.1%) and aliskiren monotherapy (73.1%) than with ramipril monotherapy (65.8%; $P < .05$).[14,17,18]

Aliskiren Added to a Calcium Channel Blocker

The antihypertensive efficacy and tolerability of aliskiren as add-on therapy to the calcium channel blocker amlodipine was assessed in a double-blind, randomized, active-controlled, parallel-group study. Patients with mild-to-moderate hypertension were treated with amlodipine, 5 mg once daily for a 4-week period. Those who did not achieve a diastolic BP ≤ 90 mm Hg (n = 545) were randomized to receive 1) addition of aliskiren 150 mg (n = 187); or 2) continued treatment with amlodipine 5 mg (n = 180); or 3) increase in amlodipine dose to 10 mg once daily (n = 178). The primary efficacy endpoint was the change in msDBP after an additional 6-week treatment period.[15]

As shown in Figure 4, the addition of aliskiren 150 mg to amlodipine 5 mg produced significantly greater reductions in msDBP and msSBP

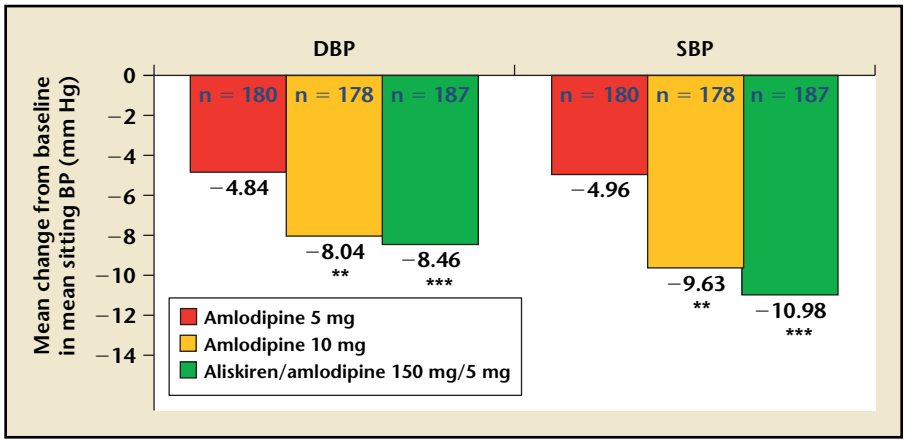


Figure 4. *Effect of amlodipine alone and in combination with aliskiren in patients not achieving target blood pressure (BP) after monotherapy with amlodipine 5 mg. Aliskiren significantly improves BP control when added to amlodipine 5 mg. DBP, diastolic blood pressure; SBP, systolic blood pressure. **P = .002, ***P < .0001 vs amlodipine 5 mg. Data from Munger et al.*[14]

than continued amlodipine 5 mg monotherapy ($P < .0001$ for both msDBP and msSBP vs amlodipine 5 mg). The BP reductions achieved with combination therapy were not significantly different from the reductions achieved by increasing the dosage of amlodipine to 10 mg once daily. Responder rates were highest with the aliskiren/amlodipine combination (64.2%). Treatment-related peripheral edema was reported more frequently with amlodipine 10 mg (11.2%) than with amlodipine 5 mg (3.4%) or combination therapy (2.1%).[15]

Discussion

Several important issues must be addressed when evaluating any new agent for the treatment of hypertension. Characterization of the pharmacokinetics and pharmacodynamics determines the duration of drug action and the necessary dosing frequency. The potency of an agent in terms of BP reduction is paramount, and the dose–response relationship of drug compared with placebo is used to select the most clinically useful doses. Direct comparison with available antihypertensive drugs is required to ascertain the potency of an agent relative to that of existing therapies, and the efficacy of the drug in combination with other agents is critical in an era when combination therapy is a practical necessity in the treatment of most patients with significant hypertension. The safety of a new agent is an issue of overriding importance. The type and frequency of short-term side effects, tolerability during long-term use, and the presence or absence of rebound effects following drug discontinuation are essential components of a drug's utility profile. When the first agent in a new class is assessed, the task is complicated by the lack of an existing database on drugs with a similar mechanism of action.

From the extensive database on aliskiren acquired to date, it is clear that this drug is an effective antihypertensive agent with a long therapeutic half-life suitable for once-daily administration. In clinical trials, once-daily dosing resulted in dose-dependent systolic and diastolic BP reduction up to a dose of 300 mg once daily.[7] In 1 study, a small additional reduction in BP was seen at a dose of 600 mg once daily.[11] Overall, 150 and 300 mg seem to be the most clinically useful doses. Studies that used ambulatory BP monitoring demonstrated BP reduction throughout the 24-hour dosing period, and trough-to-peak ratios up to 98% have been observed with the 300-mg dose.[11] No attenuation in BP reduction has been observed in patients maintained on aliskiren for periods of up to 11 months.[16]

In comparative studies, aliskiren demonstrates potency for BP reduction approximately equal to that of other blockers of the renin-angiotensin system. When compared with the ARBs losartan and irbesartan, aliskiren at a dose of 300 mg proved comparable to losartan 100 mg, and aliskiren at a dose of 150 mg produced BP reductions similar to those with irbesartan 150 mg.[7,13] The reduction in systolic BP with aliskiren 300 mg was somewhat superior to that produced by the ACE inhibitor ramipril at a dose of 10 mg once daily; however, no difference was observed in the effect on diastolic BP.[14] When used as monotherapy, aliskiren also showed BP reduction similar to that with low-dose HCTZ, at doses of 12.5 and 25 mg once daily.[12]

In comparative studies, aliskiren demonstrates potency for BP reduction approximately equal to that of other blockers of the renin-angiotensin system.

The short-term safety profile of aliskiren at doses of 150 and 300 mg is similar to that seen with the ARBs losartan and irbesartan.[7,13] At these doses, the tolerability profile of aliskiren was indistinguishable from placebo. At the 600-mg dose, a higher incidence of diarrhea

was observed.[7] Studies comparing aliskiren with other drug classes showed its superior tolerability, with a lower incidence of cough compared with ACE inhibitors, a lower incidence of hypokalemia compared with low-dose diuretics, and a lower incidence of peripheral edema compared with the calcium channel blocker amlodipine.[12,14,15,17,18] The safety of aliskiren alone and in combination with HCTZ has been documented in patients receiving the drug for periods of up to 1 year.[16] No rebound hypertension has been detected after either short- or long-term administration. Notably, several studies have found that, compared with placebo levels, BP reduction persists for periods of up to 4 weeks.[11,16]

More than two thirds of patients with hypertension require 2 or more antihypertensive agents to achieve the BP goals specified in current treatment guidelines.[19] Due to their complementary pharmacologic mechanisms, drugs that block the renin-angiotensin system are often administered in combination with low-dose diuretics and calcium channel blockers. In studies conducted to date, aliskiren has demonstrated additional BP reduction when combined with HCTZ at doses up to 25 mg daily.[12,16] The addition of aliskiren for patients not achieving their goal BP with amlodipine 5 mg resulted in significant additional BP lowering. The BP-reducing effect of the combination was similar to that seen when amlodipine was titrated to a dose of 10 mg. However, the tolerability profile was improved with the combination, with a lower incidence of edema, a common dose-limiting side effect of treatment with calcium channel blockers.[15]

The addition of aliskiren for patients not achieving their goal BP with amlodipine 5 mg resulted in significant additional BP lowering.

Because renin inhibitors suppress the RAS through a different mechanism than ACE inhibitors and ARBs, there is considerable interest in determining whether combining aliskiren with other blockers of the RAS would further reduce BP and/or improve endpoint reduction. In a study conducted with ramipril at a dose of 10 mg, an additional diastolic BP reduction of 2 mm Hg was obtained with the aliskiren/ramipril combination compared with component monotherapies. Though statistically significant, the combined effect on BP was less than additive.[14,17,18] Whether combined RAS inhibition with aliskiren and an ACE inhibitor or ARB will provide end organ protection beyond that predicted by BP reduction alone is the subject of considerable interest. Studies evaluating the efficacy of aliskiren in combination with the ARB valsartan are in progress.

The RAS is self-regulating and controlled via negative feedback inhibition. Stimulation of the AT_1 receptor by the RAS effector molecule angiotensin II reduces renin release from the kidney. Because both ACE inhibitors and ARBs interfere with this negative feedback loop and increase plasma renin activity, these agents promote RAS activation even

Main Points

- Aliskiren is a potent, highly specific renin inhibitor with high bioavailability and a long plasma half-life, making it suitable for once-daily administration.
- In 5 placebo-controlled clinical trials in patients with mild-to-moderate essential hypertension, once-daily aliskiren was statistically superior to placebo in reducing mean systolic and diastolic blood pressure (BP).
- In 2 dose-ranging trials comparing the efficacy and safety of aliskiren with the angiotensin receptor blockers (ARBs) losartan and irbesartan, aliskiren was comparable to both ARBs in BP-lowering effects.
- In studies comparing aliskiren with the angiotensin-converting enzyme inhibitor ramipril, aliskiren produced better systolic BP reduction.
- Studies comparing aliskiren and the low-dose diuretic hydrochlorothiazide (HCTZ) showed comparable BP reductions.
- In studies of aliskiren combined with HCTZ, 7 of the 8 dose combinations resulted in superior BP reduction compared with aliskiren or HCTZ monotherapies.
- Aliskiren and ramipril combination therapy produced greater diastolic BP reductions than aliskiren alone.
- Adding aliskiren to the calcium channel blocker amlodipine in patients not achieving their goal BP with amlodipine 5 mg resulted in additional BP lowering.

as they produce downstream suppression of its physiologic effects. Aliskiren, in contrast, suppresses plasma renin activity when given alone or in combination with other RAS blockers. Whether this will result in superior effects on end organ damage and clinical cardiovascular endpoints is as yet unknown. Studies designed to evaluate this aspect of the therapeutic efficacy of aliskiren for patients with hypertension are in progress and are planned.[1,2,6,7] ■

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