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Aliskiren Reduces Blood Pressure and Suppresses Plasma Renin Activity in Combination With a Thiazide Diuretic, an Angiotensin-Converting Enzyme Inhibitor, or an Angiotensin Receptor Blocker

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Abstract—Thiazide diuretics, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers all cause reactive rises in plasma renin activity. We hypothesized that renin inhibition with aliskiren would prevent this reactive rise and also enhance blood pressure lowering. In 3 open-label studies in which blood pressure was assessed with ambulatory measurement, aliskiren was administered to patients with mild-to-moderate hypertension in combination with hydrochlorothiazide (n=23), ramipril (n=21), or irbesartan (n=23). In the diuretic combination study, the addition of 25 mg of hydrochlorothiazide to 150 mg of aliskiren daily for 3 weeks significantly lowered daytime pressure, compared with aliskiren monotherapy (systolic/diastolic mean change from baseline [SEM]: daytime: $-18.4 [2.1]/-10.6 [1.7]$ versus $-10.4 [1.8]/-5.8 [1.4]$; nighttime: $-15.6 [2.7]/-8.1 [1.8]$ versus $-8.8 [2.9]/-5.0 [2.2]$). In the angiotensin-converting enzyme inhibitor combination study, the addition of 75 or 150 mg of aliskiren to 5 mg of ramipril alone for 3 weeks further lowered both daytime and nighttime pressures compared with ramipril monotherapy (daytime: $-10.5 [2.9]/-8.1 [2.1]$ and $-14 [3.7]/-8.7 [2.3]$ versus $-6.1 [2.4]/-5.9 [1.5]$; nighttime: $-8.1 [2.6]/-5.3 [2.4]$ and $-9.6 [3.4]/-5.3 [2.4]$ versus $-2 [2.3]/-0.7 [2.2]$). In the angiotensin receptor blocker combination study, the addition of 75 or 150 mg of aliskiren to 150 mg of irbesartan alone, for 3 weeks, resulted in significantly lower nighttime pressures compared with irbesartan monotherapy (daytime: $-14.8 [2]/-8.2 [1.3]$ and $-13.3 [1.6]/-6.8 [0.9]$ versus $-11.4 [1.6]/-6.5 [1.1]$; nighttime: $-16.1 [2.4]/-8.6 [1.7]$ and $-13.2 [2.7]/-7.2 [1.9]$ versus $-9.0 [2.5]/-4.7 [1.9]$). Aliskiren (150 mg) alone significantly inhibited plasma renin activity by 65% ($P < 0.0001$). Ramipril and irbesartan monotherapy caused 90% and 175% increases in plasma renin activity, respectively. By contrast, when aliskiren was coadministered with hydrochlorothiazide, ramipril, or irbesartan, plasma renin activity did not increase but remained similar to baseline levels or was decreased (combination therapy versus untreated; median [interquartile range]; aliskiren and hydrochlorothiazide: $0.4 [0.2 \text{ to } 1.1]$ versus $0.7 [0.5 \text{ to } 1.3]$; ramipril and aliskiren: $0.5 [0.3 \text{ to } 0.9]$ versus $0.6 [0.5 \text{ to } 0.8]$; irbesartan and aliskiren: $0.4 [0.2 \text{ to } 0.9]$ versus $0.6 [0.4 \text{ to } 0.9]$). These results suggest that renin inhibition with aliskiren in these combinations increases renin-angiotensin system suppression, improves 24-hour blood pressure control, and may ultimately provide better end-organ protection in patients with hypertension. (*Hypertension*. 2007;49:276-284.)

Key Words: aliskiren ■ ambulatory blood pressure measurement ■ combination therapy ■ hypertension ■ plasma renin activity ■ renin inhibitor ■ renin-angiotensin-aldosterone system

Activation of the renin-angiotensin (Ang)-aldosterone system (RAAS) plays an important role in the development of hypertension and end-organ damage.¹ Indeed, pre-treatment plasma renin activity (PRA) has been shown to be a risk factor for myocardial infarction in hypertensive patients.^{2,3} RAAS suppression is, therefore, an important goal of antihypertensive therapy, and RAAS inhibitors, such as

Ang-converting enzyme (ACE) inhibitors and Ang receptor blockers (ARBs), have proven to be highly successful treatments for hypertension, heart failure, and related cardiovascular disorders.⁴

However, optimized RAAS suppression is difficult to achieve with currently available antihypertensive agents, because ACE inhibitors, ARBs, and diuretics all activate compen-

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satory feedback mechanisms that result in renin release and increased PRA.^{5,6} ACE inhibitors cause an increase in PRA and Ang I, which is then available for conversion to Ang II by both remaining unblocked ACE and by ACE-independent pathways,⁷ whereas ARBs and diuretics increase PRA, Ang I, and Ang II. By contrast, renin inhibitors neutralize any compensatory increase in PRA and prevent the formation of both Ang I and Ang II.⁸

Although a variety of potential renin inhibitors have been developed, their low potency and/or poor pharmacokinetic profiles prevented these compounds from being developed for clinical use.^{9,10} Aliskiren, the first in a new class of orally effective renin inhibitors for the treatment of hypertension, is a potent and specific inhibitor of human renin *in vitro* with an IC_{50} in the low nanomolar range.^{11–13} Once-daily oral doses of aliskiren of ≤ 640 mg caused dose-dependent and sustained RAAS inhibition with excellent tolerability in healthy volunteers,¹⁴ whereas recent studies in patients with mild-to-moderate hypertension have shown that aliskiren provides antihypertensive efficacy and safety at least equivalent to the ARBs losartan and irbesartan.^{15,16}

The aim of the 3 open-label studies presented in this article was to investigate the antihypertensive efficacy of aliskiren, when combined with a diuretic (hydrochlorothiazide [HCTZ]), an ACE inhibitor (ramipril), or an ARB (irbesartan) in patients with mild-to-moderate hypertension. Ambulatory blood pressure measurement (ABPM) was used to assess the effects of aliskiren throughout the 24-hour dosing interval, and the effects of aliskiren on PRA were also investigated to examine whether RAAS suppression was optimized in combination with agents known to stimulate PRA.

Methods

Participants

Men and women, aged 18 to 80 years, with off-treatment average daytime systolic ABPM ≥ 140 and ≤ 180 mm Hg, who were otherwise in good health, were eligible for entry into the studies. Patients had to be previously untreated or to be receiving only antihypertensive monotherapy; women had to be postmenopausal, surgically sterile, or using appropriate contraception. Patients were ineligible for inclusion if current antihypertensive medications could not be withdrawn or if they had secondary hypertension, malignant hypertension, coronary artery disease, cerebrovascular disease, or any surgical or medical condition that might significantly alter the absorption, distribution, metabolism, or excretion of study medications.

The studies were conducted in accordance with Good Clinical Practice, the Declaration of Helsinki of the World Medical Association, and EC Directive 91/507. All of the subjects gave written informed consent. The study protocols were approved by local and central institutional review boards and by the appropriate local research ethics committees.

Study Design

It was planned to recruit 18 to 24 patients to each of the 3 open-label studies. In each, a screening visit was followed by a 7- to 10-day washout period, during which antihypertensive treatment was discontinued. A baseline 24-hour ABPM was then recorded before commencement of study treatments. The screening assessment included a complete medical history, physical examination, clinic blood pressure measurement, safety laboratory tests (blood hematology, blood chemistry, and urinalysis), and 12-lead electrocardiography. At baseline and at the end of each 3-week drug treatment period, adverse events, concurrent medication, and compliance with study

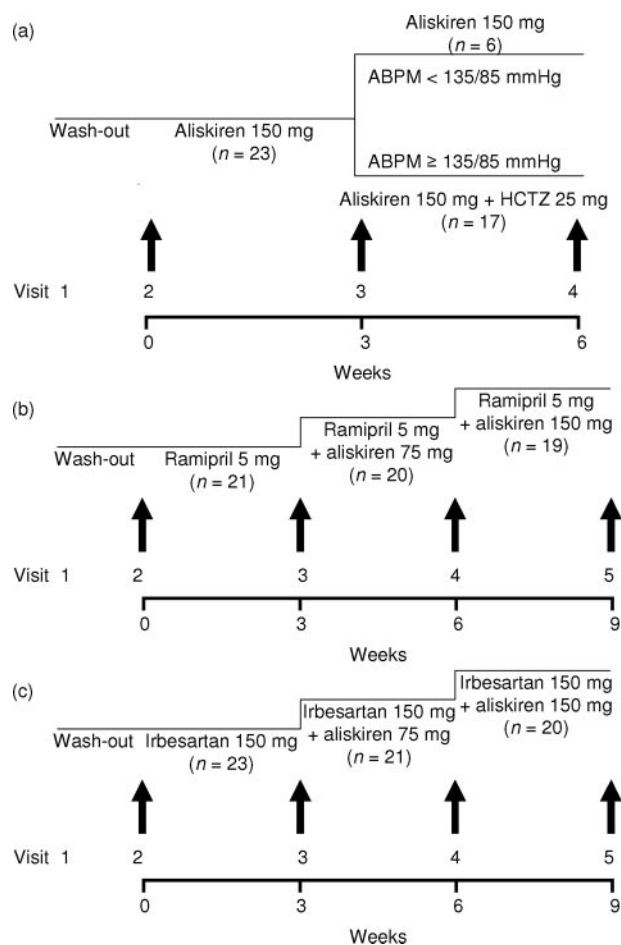


Figure 1. Design of studies investigating (a) aliskiren in combination with the diuretic, HCTZ; (b) addition of aliskiren to the ACE inhibitor ramipril; or (c) addition of aliskiren to the ARB irbesartan in patients with mild-to-moderate hypertension. ABPMs and blood samplings for plasma renin activity and aliskiren measurements are denoted by vertical arrows.

medication were recorded, in addition to clinic blood pressure measurement, ABPM, PRA, trough plasma aliskiren levels, safety laboratory tests, and electrocardiography.

Aliskiren/Diuretic Combination Study

All of the patients initially received once-daily oral treatment with aliskiren 150 mg alone for 3 weeks. Only those patients whose daytime ABPM remained $\geq 135/85$ mm Hg had 25 mg of HCTZ once daily added to their treatment regimen for a further 3 weeks. Those patients whose daytime ABPM was $< 135/85$ mm Hg continued 150 mg of aliskiren alone (Figure 1).

ACE Inhibitor/Aliskiren and ARB/Aliskiren Combination Studies

In these 2 studies, patients were initially treated with 5 mg of ramipril once daily or 150 mg of irbesartan daily for 3 weeks. Aliskiren (75 mg) once daily was then added to the ramipril or irbesartan treatment for a further 3-week period. At the end of this second treatment period, the dose of aliskiren was increased to 150 mg daily for the final 3 weeks of both studies (Figure 1).

Study Treatments

Throughout the 3 studies, patients were asked to take all of the study medication, once daily, 30 minutes before eating breakfast. Aliskiren was supplied as hard gelatin capsules for oral administration containing 82.88 or 165.75 mg of aliskiren hemifumarate, equivalent to

Patient Baseline and Demographic Characteristics

Patient Details	Aliskiren/Diuretic Combination Study (n=23)	ACE Inhibitor/Aliskiren Combination Study (n=21)	ARB/Aliskiren Combination Study (n=23)
Gender, male/female	18/5	17/4	14/9
Age, y	57.4±8.1	53.4±10.4	49.6±9.3
Height, cm	171.9±7.5	171.2±9.2	169.0±8.4
Weight, kg	82.0±10.9	83.4±12.7	86.5±18.7
Body mass index, kg/cm ²	27.8±3.7	28.4±3.7	30.1±5.3
Smoking habit, smoker/nonsmoker	3/20	3/18	11/12
Alcohol habit, drinker/nondrinker	15/8	18/3	11/12
Total cholesterol, mmol/L	5.6±0.9	5.6±1.0	5.4±0.9
Triglycerides, mmol/L	2.3±1.3	2.4±1.1	2.8±2.2
Creatinine, μmol/L	100.3±17.6	102.8±9.7	96.0±14.2
Clinic systolic blood pressure	148.4±12.5	158.4±18.1	157.0±16.5
Clinic diastolic blood pressure	88.6±7.5	88.8±9.6	88.8±9.6
Daytime systolic blood pressure	150.6±8.9	150.0±11.6	156.2±11.4
Daytime diastolic blood pressure	90.7±8.2	94.2±9.4	96.7±8.4
Nighttime systolic blood pressure	132.1±12.4	125.1±14.7	135.2±17.7
Nighttime diastolic blood pressure	76.7±7.9	73.1±13.3	79.3±11.3
Previous antihypertensive medication, yes/no	17/6	17/4	21/2

Data are presented as the mean±SD unless otherwise stated.

75 or 150 mg of active aliskiren, respectively. Other study drugs were supplied as commercially available tablets.

Blood Pressure Measurement

Sitting clinic blood pressure measurement and heart rate were measured from the right arm using a regularly calibrated validated automated sphygmomanometer (Omron HEM-705CP).¹⁷ Ambulatory measurements were made every 30 minutes throughout the 24-hour period using SpaceLabs 90207 monitors (SpaceLabs Medical Inc).¹⁸ Mean daytime (9:00 AM and 9:00 PM) and nighttime (1:00 AM and 6:00 AM) systolic and diastolic blood pressures and also heart rates were calculated from ABPMs. ABPM was regarded as satisfactory if there were ≥14 daytime readings and 8 nighttime readings.¹⁹

Assessment of PRA and Aliskiren Levels

Fasting venous blood was collected from seated patients 24 hours after the last drug intake. PRA was measured by the trapping of generated Ang I by antibodies and by subsequent radioimmunoassay.²⁰ Aliskiren was measured in 2.5 μL of plasma by direct radioimmunoassay with a limit of quantification of 0.15 ng/mL and with intra-assay and inter-assay coefficients of variation <15%.¹⁴

Statistical Methods

All of the data analyses were carried out using SAS Software (SAS Institute Inc). Analyses concerning tolerability and safety were conducted on the safety populations, namely all of the patients who received ≥1 dose of study treatment (aliskiren/diuretic combination study: n=23; ACE inhibitor/aliskiren combination study: n=21; ARB/aliskiren combination study: n=23). Analyses concerning drug efficacy were performed on the intention-to-treat population, defined as patients of the safety population who received combination therapy, and who had valid ABPMs at baseline, on monotherapy, and on combination therapy (aliskiren/diuretic combination study: n=17; ACE inhibitor/aliskiren combination study: n=20; ARB/aliskiren combination study: n=21).

For all 3 of the studies, the primary end point was the change in daytime systolic ABPM with combination therapy compared with monotherapy. Mean changes in daytime systolic ABPM were compared using random-effects ANOVA models with Bonferroni's

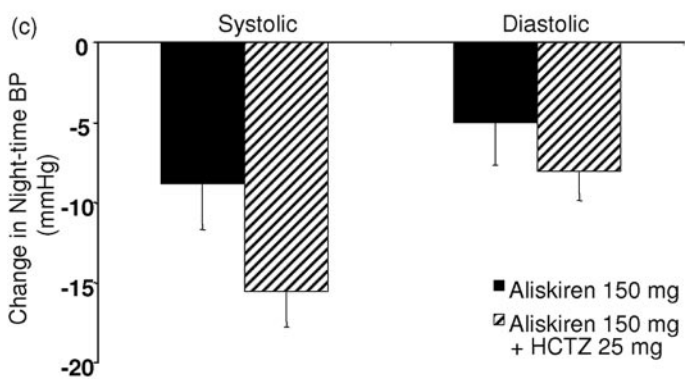
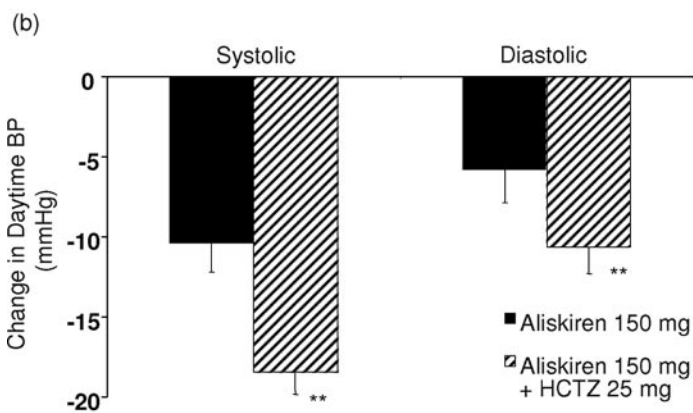
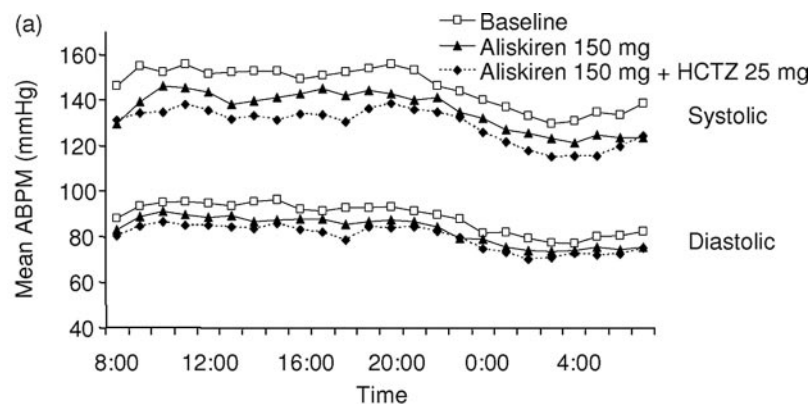
posthoc tests. Similar models were used to analyze treatment effects on secondary end points: daytime diastolic ABPM, nighttime systolic and diastolic ABPM, and daytime and nighttime heart rates. Because PRA values are not normally distributed, these were compared by Kruskal–Wallis tests with Dunn's posthoc tests.

Results**Participants**

The distributions of gender, age, body mass index, lifestyle habits, and cardiovascular risk factors among the patients in the 3 studies were similar (Table). Approximately three fourths of patients in each study were men and between 50 and 60 years old; all of the patients were white. The majority of patients in all 3 of the studies had previously received antihypertensive medication, of which ACE inhibitors and β-blockers were the most common agents.

Effect of Aliskiren Monotherapy and Combination Treatment on ABPM**Aliskiren/Diuretic Combination Study**

At baseline, overall mean daytime systolic ABPM (mean±SD) was 150.6±8.9 mm Hg (n=23). After 3 weeks of treatment with 150 mg of aliskiren, mean daytime systolic ABPM remained above 135/85 mm Hg in 17 of the 23 patients (142.4±9.4 mm Hg). HCTZ (25 mg) was added to aliskiren treatment in these patients for 3 weeks, and this led to a significant decrease in mean daytime systolic ABPM to 133.8±7.0 mm Hg ($P=0.0007$; n=17; Figure 2a and 2b). The aliskiren/HCTZ combination also significantly lowered daytime diastolic ABPM compared with aliskiren monotherapy ($P=0.0006$; Figure 2b). Changes in nighttime systolic and diastolic ABPM followed similar trends but just failed to achieve standard statistical significance ($P=0.06$ and $P=0.09$; Figure 2c). No changes in heart rate were observed



** P<0.001 compared with aliskiren 150 mg

Figure 2. Effects of aliskiren alone or in combination with HCTZ on (a) mean 24-hour systolic and diastolic ambulatory blood pressure profiles, (b) mean daytime systolic and diastolic ABPM, and (c) mean nighttime systolic and diastolic ABPM. In b and c, bars indicate the change in blood pressure from baseline (mean±SE) after treatment with 150 mg of aliskiren (filled bars) or 150 mg of aliskiren plus 25 mg of HCTZ (striped bars).

with aliskiren treatment, either as monotherapy or in combination with HCTZ.

ACE Inhibitor/Aliskiren Combination Study

Treatment with 5 mg of ramipril for 3 weeks resulted in a decrease in mean daytime systolic ABPM from 149.5±11.2 mm Hg at baseline to 143.4±11.1 mm Hg. Mean daytime systolic ABPM fell further to 139.4±12.7 mm Hg with the addition of 75 mg of aliskiren for 3 weeks ($P=0.03$ compared with ramipril monotherapy) and tended to further reduce when the dose of aliskiren was increased to 150 mg (136.4±10.9 mm Hg; $P=0.0006$) compared with ramipril monotherapy, but P not significant compared with 5 mg of ramipril plus 75 mg of aliskiren (Figure 3a and 3b). Mean daytime diastolic ABPM was also significantly reduced by the addition of 150 mg of aliskiren to 5 mg of ramipril daily (Figure 3b), as were nighttime systolic and diastolic ABPM

pressures by both aliskiren doses (Figure 3c). Ramipril alone or in combination with aliskiren had no effect on heart rate.

ARB/Aliskiren Combination Study

Irbesartan monotherapy reduced systolic and diastolic daytime and nighttime ABPM (Figure 4a through 4c). There was a trend for mean daytime pressures to decrease with the addition of 75 mg of aliskiren, but this trend was not statistically significant (Figure 4b). However, the addition of 75 mg of aliskiren to 150 mg of irbesartan did provide significantly greater reductions in nighttime systolic and diastolic ABPM compared with irbesartan monotherapy ($P<0.05$; Figure 4c). There was a trend for both daytime and nighttime pressures to rise rather than fall when the dose of aliskiren was increased from 75 to 150 mg daily. However, none of these changes was statistically significant. Irbesartan alone or in combination with aliskiren had no effect on heart rate.

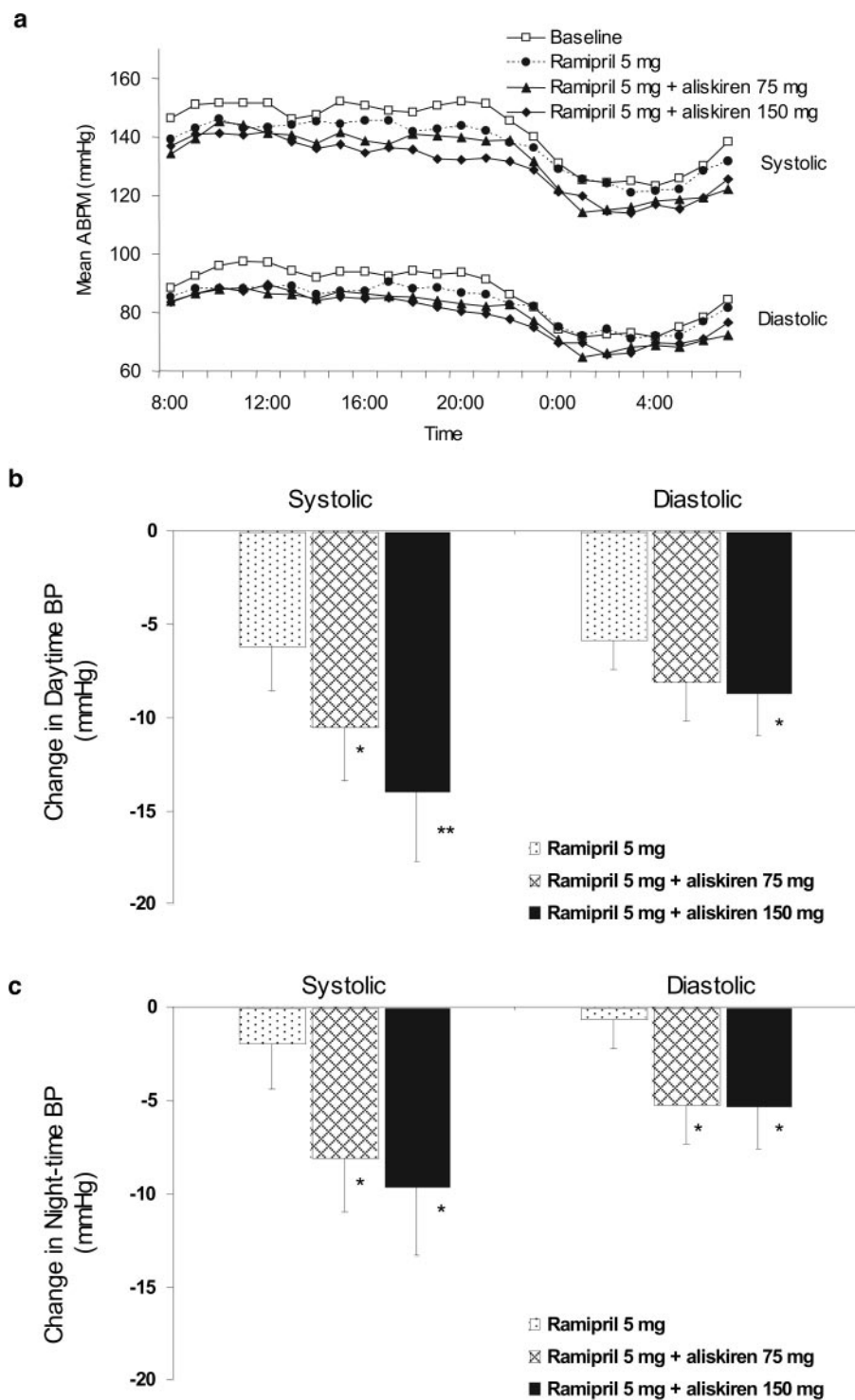


Figure 3. Effects of ramipril alone or in the presence of aliskiren on (a) mean 24-hour systolic and diastolic ambulatory blood pressure profiles, (b) mean daytime systolic and diastolic ABPM, and (c) mean nighttime systolic and diastolic ABPM. In b and c, bars indicate the change in blood pressure from baseline (mean±SE) after treatment with 5 mg of ramipril (stippled bars), ramipril plus 75 mg of aliskiren (hatched bars) or ramipril plus 150 mg of aliskiren (filled bars).

* P<0.05 compared with ramipril 5 mg

** P<0.001 compared with ramipril 5 mg

Effect of Aliskiren Alone and in Combination on PRA

In the aliskiren/diuretic combination study, initial treatment with 150 mg of aliskiren alone significantly inhibited PRA by 65% ($P<0.0001$). In the ACE inhibitor/aliskiren and the ARB/aliskiren combination studies, ramipril and irbesartan

monotherapy resulted in 90% and 175% increases, respectively, in PRA. By contrast, when aliskiren was coadministered with HCTZ, ramipril, or irbesartan, PRA levels were similar to or less than baseline untreated levels (combination therapy versus untreated: median [interquartile range]; aliskiren 150 mg plus HCTZ 25 mg: 0.4 [0.2 to 1.1] versus

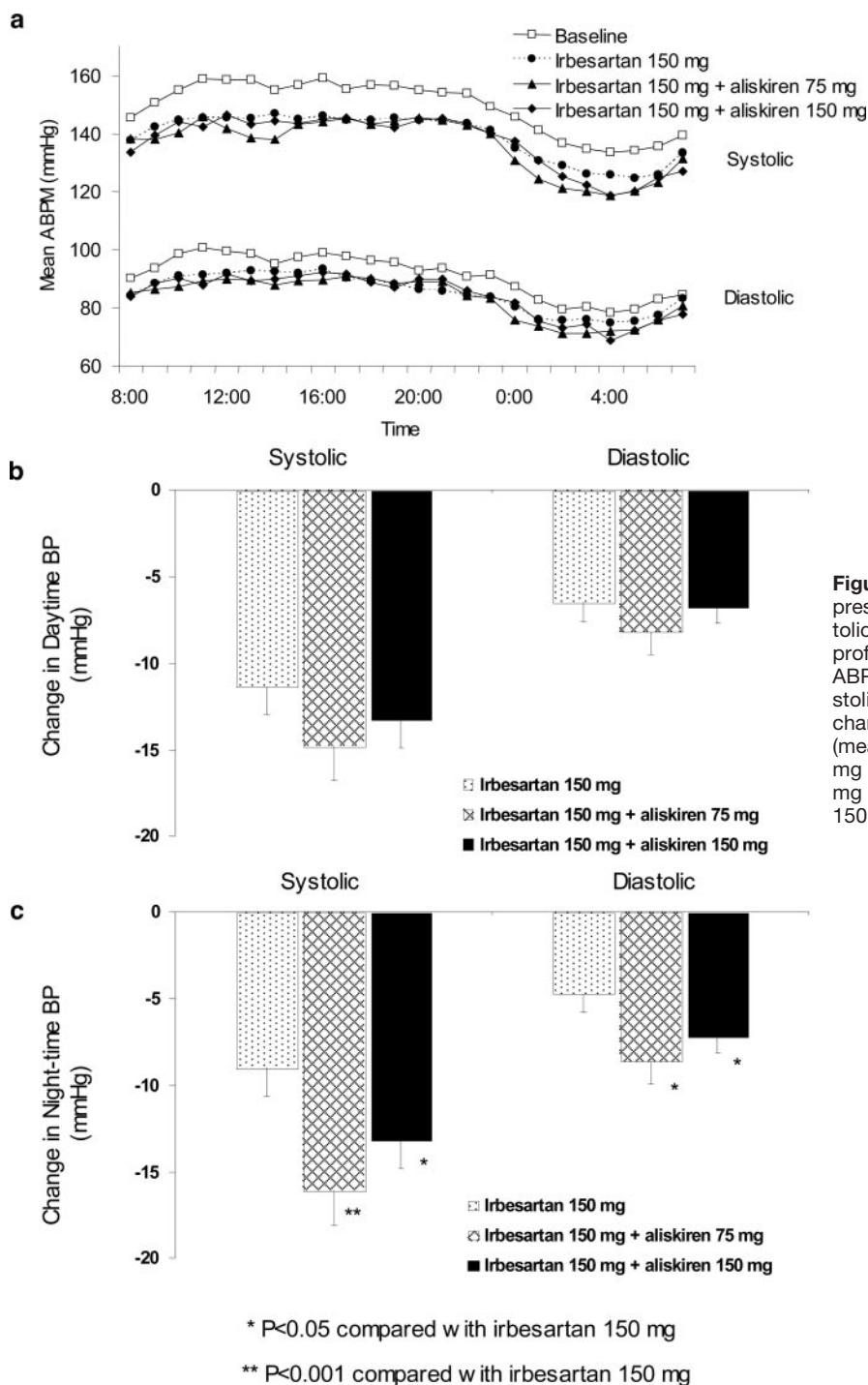


Figure 4. Effects of irbesartan alone or in the presence of aliskiren on (a) mean 24-hour systolic and diastolic ambulatory blood pressure profiles, (b) mean daytime systolic and diastolic ABPM, and (c) mean nighttime systolic and diastolic ABPM. In b and c, bars indicate the change in blood pressure from baseline (mean±SE) after treatment with irbesartan 150 mg (stippled bars), irbesartan plus aliskiren 75 mg (hatched bars), or irbesartan plus aliskiren 150 mg (filled bars).

0.7 [0.5 to 1.3]; ramipril 5 mg plus aliskiren 75 mg: 0.6 [0.4 to 1.8]; ramipril 5 mg plus aliskiren 150 mg: 0.5 [0.3 to 0.9] versus 0.6 [0.5 to 0.8]; irbesartan 150 mg plus aliskiren 75 mg: 0.5 [0.4 to 1.1]; irbesartan 150 mg plus aliskiren 150 mg: 0.4 [0.2 to 0.9] versus 0.6 [0.4 to 0.9]; Figure 5). We also explored whether the changes in blood pressure that were observed with each treatment addition correlated with changes in PRA. In the aliskiren/diuretic and ACE inhibitor/aliskiren combination studies, changes in pressures tended to correlate directly with the change in PRA with commencement of 150 mg of aliskiren daily and with increasing

aliskiren dosage from 75 to 150 mg daily, respectively (Figures I and II available online at <http://hyper.ahajournals.org>). By contrast, no such association was observed when aliskiren dosage was increased from 75 to 150 mg daily in the ARB/aliskiren study (Figure III).

Plasma Concentrations of Aliskiren Alone and During Combination Therapy

Aliskiren/Diuretic Combination Study

The mean aliskiren plasma concentration at visit 3, after treatment for 3 weeks with 150 mg of aliskiren, was

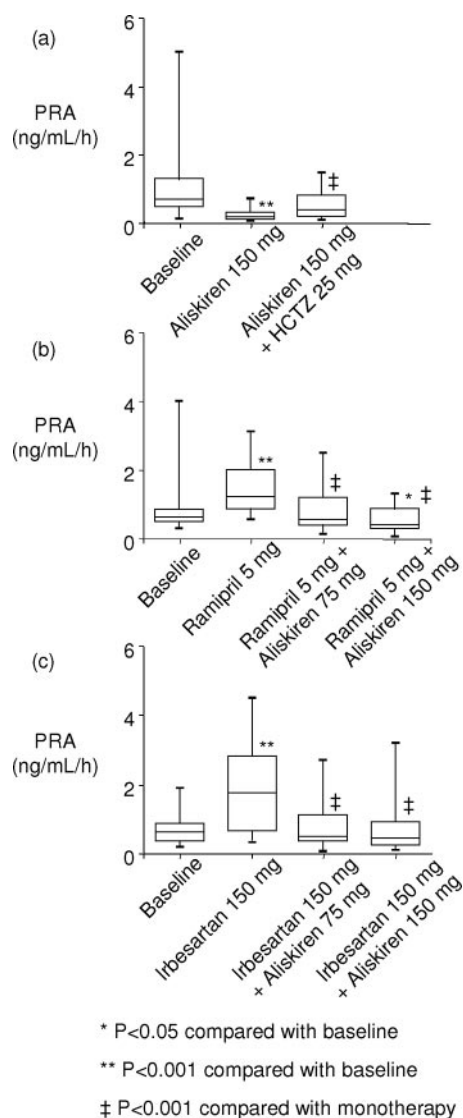


Figure 5. Effects on plasma renin activity of (a) aliskiren alone or in the presence of HCTZ, (b) ramipril alone or in the presence of aliskiren, or (c) irbesartan alone or in the presence of aliskiren in patients with mild-to-moderate hypertension. Values are presented as the median, interquartile range, and range.

15.0±10.8 ng/mL (n=23). No significant differences in the plasma concentrations of aliskiren at week 6 were observed between patients who continued on 150 mg of aliskiren alone (10.7±6.7 ng/mL) and those who received aliskiren and 25 mg of HCTZ (13.1±8.3 ng/mL).

Aliskiren/ACE Inhibitor Combination Study

A dose-dependent increase in plasma levels of aliskiren was observed in this study; mean trough plasma concentrations of aliskiren were 3.9±2.6 ng/mL (n=20) after 3 weeks of treatment with 75 mg of ramipril/aliskiren and 9.5±5.9 ng/mL (n=19) after a further 3 weeks of treatment with 150 mg of ramipril/aliskiren.

ARB/Aliskiren Combination Study

Similarly, plasma levels of aliskiren reflected the administered dosage in this study: mean trough plasma concentrations of aliskiren were 3.3±1.7 ng/mL (n=22) after 3

weeks of treatment with 75 mg of irbesartan/aliskiren and 7.6±3.2 ng/mL (n=19) after 3 weeks of treatment with 150 mg of irbesartan/aliskiren.

Compliance, Safety, and Tolerability of Aliskiren Monotherapy and Combination Treatment

Compliance, assessed from counts of returned capsules, averaged >95% in all of the treatment periods of all 3 studies. Aliskiren was well tolerated either as monotherapy or in combination. A total of 11 adverse events were recorded in 5 patients in the aliskiren/HCTZ study, 25 adverse events in 10 patients in the ramipril/aliskiren study, and 30 adverse events in 17 patients in the irbesartan/aliskiren study (Table I). Only 2 adverse events were rated as severe: 1 myocardial infarction in a patient receiving irbesartan and 150 mg of aliskiren and headaches in a patient receiving ramipril monotherapy. Overall, there were no clinically significant changes in laboratory parameters at consecutive visits during the course of any of these studies. The maximum individual serum potassium levels recorded when aliskiren was coadministered with ramipril and with irbesartan were 5.3 and 5.5 mmol/L, respectively (see Table II).

Discussion

The 3 open-label studies reported here investigated whether the antihypertensive effects of aliskiren, a novel, orally effective renin inhibitor, would be increased in combination with a thiazide diuretic and whether aliskiren would provide additional blood pressure lowering in patients with mild-to-moderate hypertension when administered in combination with an ACE inhibitor or with an ARB. Because of the sequential nature of the studies, noninvasive 24-hour ABPM was used to monitor blood pressure, because placebo response and regression to the mean are minimal or absent with this method of blood pressure measurement.²¹

Potential of the blood pressure-lowering effect of HCTZ by an early generation renin inhibitor, remikiren, had already been demonstrated, but in that study it was notable that remikiren alone exerted no significant antihypertensive effect.²² By contrast, in our diuretic combination study, monotherapy with 150 mg of aliskiren for 3 weeks significantly lowered daytime systolic ABPM in patients with mild-to-moderate hypertension, and the addition of 25 mg of HCTZ daily to aliskiren treatment led to further significant reductions in daytime systolic and diastolic ABPM. Importantly, the ABPM profiles clearly showed that aliskiren monotherapy and aliskiren in combination with HCTZ provided sustained blood pressure reductions throughout the 24-hour dosing interval. These results likely reflect the long plasma half-life of aliskiren¹⁴ and are consistent with the results of previous studies.^{15,16}

Results of a recent preclinical study suggested that aliskiren could potentiate the antihypertensive effects of an ACE inhibitor in spontaneously hypertensive rats.¹³ Our article is the first to report the effects of combinations of renin inhibition and downstream RAAS inhibition on blood pressure in humans. The addition of aliskiren to ramipril resulted in significant reductions in both daytime and nighttime systolic and diastolic pressures. Although the addition of aliskiren to irbesartan seemed to lower

both daytime and nighttime ABPM, only the nocturnal reductions were statistically significant.

The consistent lowering of nocturnal blood pressures by all 3 of the combination therapies may have particular relevance in view of recent evidence that nocturnal blood pressures predict cardiovascular mortality more powerfully than either clinic or daytime ambulatory pressures.²³ However, it should be noted that submaximal doses of both ramipril and irbesartan were used in these studies. Therefore, any additional blood pressure lowering seen with combination therapy may equally have occurred if the dosage of the ACE inhibitor or the ARB had been increased.

Aliskiren (150 mg), when administered in combination with valsartan (160 mg) to salt-depleted healthy volunteers, has already been reported to suppress the compensatory rise in PRA that would normally be observed during ARB monotherapy.²⁴ In the current studies, PRA in hypertensive patients taking any of the 3 combinations was either similar to or less than baseline untreated values. The fact that the feedback-induced increase in PRA and Ang I seen with diuretics, ACE inhibitors, and ARBs does not occur during renin inhibition may have potentially favorable consequences. A relationship between PRA and the risk of myocardial infarction in patients with hypertension was first identified by a retrospective analysis conducted >30 years ago.^{25,26} Recent studies have provided additional evidence that PRA is a predictor of cardiovascular risk.^{2,3} Although these findings are likely to be at least in part because of Ang II-mediated effects, such as increased blood pressure, and effects on atherosclerosis,²⁷ increased renin or prorenin could also directly increase cardiovascular risk through enhanced stimulation of the newly discovered renin/prorenin receptor, the full effect of which remains to be established.²⁸

Conversely, there is evidence that Ang-(1-7) contributes to the antihypertensive actions of both ACE inhibitors and ARBs.^{29,30} Renin inhibition would be expected to reduce formation of Ang-(1-7), and, therefore, the addition of renin inhibition to ACE inhibition or ARB could potentially diminish blood pressure lowering. Indeed, the trend for a rise in pressures in the ARB/aliskiren combination study, when the dosage of aliskiren was increased from 75 to 150 mg daily, and the lack of correlation with changes in blood pressure with changes in PRA, suggests that further studies of this combination of agents are certainly warranted, with both greater patient numbers and a wider range of doses. Because a similar phenomenon could also occur when higher doses of aliskiren and an ACE inhibitor are combined, further studies are also advisable.

The good tolerability of aliskiren in these 3 small studies, whether administered alone or in combination with HCTZ, ramipril, or irbesartan, is consistent with other larger studies demonstrating a safety profile for aliskiren equivalent to that of ARBs,^{15,16} a drug class well known for their placebo-like tolerability. A low likelihood of adverse effects would be expected for aliskiren, because renin has a high specificity for its substrate, angiotensinogen.¹⁰ Moreover, renin inhibitors do not affect substance P or kinin metabolism and, hence, would not be expected to cause dry cough or angioneurotic edema, which are characteristic adverse effects of ACE inhibitors.³¹ The addition of 25 mg of HCTZ to 150 mg of

aliskiren did not seem to alter plasma aliskiren levels. Plasma concentrations of aliskiren administered in combination with ramipril or with irbesartan were similar to those observed after aliskiren monotherapy at doses of 75 and 150 mg in previous studies.^{15,16} These results suggest that it is unlikely that any clinically significant pharmacokinetic interactions occur between aliskiren and HCTZ, between aliskiren and ramipril, or between aliskiren and irbesartan.

Clinical Perspective

The studies reported here show that the novel, orally effective renin inhibitor aliskiren provides 24-hour antihypertensive effects that may be increased by the addition of the diuretic, HCTZ, and that combining aliskiren with the ACE inhibitor, ramipril, or with the ARB, irbesartan, provides significantly greater reductions in blood pressure than with monotherapy. Aliskiren treatment, whether administered alone or in combination with HCTZ, ramipril, or irbesartan, was well tolerated. In addition, aliskiren in combination therapy effectively neutralizes the compensatory rise in PRA that is stimulated by existing antihypertensive agents and, therefore, offers the prospect of optimized RAAS suppression in patients with hypertension. It remains to be seen whether these treatment combinations will provide greater protection from cardiovascular morbidity and mortality.

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