

Hypertension

Aliskiren, an Oral Renin Inhibitor, Provides Dose-Dependent Efficacy and Sustained 24-Hour Blood Pressure Control in Patients With Hypertension

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- Objectives** This dose-ranging study evaluated the antihypertensive efficacy and tolerability of aliskiren in patients with mild-to-moderate hypertension.
- Background** Low blood pressure (BP) control rates among patients with hypertension indicate a need for improved treatment options. This study investigates aliskiren, the first in a new antihypertensive class called renin inhibitors.
- Methods** Patients with mean sitting diastolic BP 95 to 109 mm Hg were randomized to aliskiren 150, 300, or 600 mg or placebo once daily for 8 weeks. Patients completing this treatment phase entered a 2-week treatment-free withdrawal period. Office BP was recorded at baseline, weeks 2, 4, 6, and 8 of treatment, and 4 days and 2 weeks after cessation of treatment. A subgroup of patients underwent ambulatory BP monitoring.
- Results** In total, 672 patients were randomized to treatment. After 8 weeks, aliskiren 150, 300, and 600 mg significantly reduced mean sitting BP (systolic/diastolic) by 13.0/10.3, 14.7/11.1, and 15.8/12.5 mm Hg, respectively, versus 3.8/4.9 mm Hg with placebo (all $p < 0.0001$ for systolic and diastolic BP). The BP-lowering effect of aliskiren persisted for up to 2 weeks after treatment withdrawal. Aliskiren significantly reduced mean 24-h ambulatory BP ($p < 0.0001$ vs. placebo with all doses) exhibiting smooth, sustained effects and high trough-to-peak ratios. Aliskiren was well tolerated; overall adverse event rates were 40.1%, 46.7%, and 52.4% with aliskiren 150, 300, and 600 mg, respectively, and 43.0% with placebo. Few patients discontinued treatment due to adverse events.
- Conclusions** Aliskiren provides significant antihypertensive efficacy in patients with hypertension, with no rebound effects on blood pressure after treatment withdrawal. (J Am Coll Cardiol 2007;49:1157–63) © 2007 by the American College of Cardiology Foundation

Aliskiren is the first in a new class of orally effective renin inhibitors and is a potent inhibitor of human renin (1). Aliskiren has a half-life of approximately 40 h (2,3), making it suitable for once-daily dosing, with less potential for loss of efficacy between doses than shorter-acting agents. Continuous 24-h blood pressure (BP) control throughout the dosing period is clinically important, as it can reduce BP variability that may be suboptimally controlled in other drug classes (4–6).

Previous clinical trials of aliskiren in patients with mild-to-moderate hypertension have demonstrated BP lowering at least comparable with the angiotensin receptor blockers (ARBs) irbesartan and losartan (7,8), with placebo-like tolerability (7). Consistent with its mechanism of action, aliskiren has also been shown to reduce plasma renin activity (PRA) from baseline, both in hypertensive patients and in healthy volunteers (9,10).

See page 1164

In this dose-ranging study, we further evaluated the antihypertensive efficacy of aliskiren at doses of 150 to 600 mg in patients with mild-to-moderate essential hypertension. We also assessed safety and tolerability, and the effects of aliskiren on PRA and renin concentration (RC). Monitoring of BP, PRA, and RC continued after cessation of aliskiren treatment to detect any potential rebound effect.

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Abbreviations and Acronyms

ABPM = ambulatory blood pressure monitoring

AE = adverse event

ARB = angiotensin receptor blocker

BP = blood pressure

ITT = intent-to-treat

LSM = least squares mean

maDBP/maSBP = mean ambulatory diastolic/systolic blood pressure

msDBP/msSBP = mean sitting diastolic/systolic blood pressure

PRA = plasma renin activity

RC = renin concentration

Methods

Participants. Men and women age ≥ 18 years with mild-to-moderate essential hypertension (mean sitting diastolic blood pressure [msDBP] ≥ 95 and < 110 mm Hg) were recruited at 68 centers internationally.

Subjects were excluded from the study if they had severe hypertension (msDBP ≥ 110 mm Hg) or secondary hypertension; a history of serious cardiac or cerebrovascular disease; type 1 or 2 diabetes mellitus with poor glycemic control (glycosylated hemoglobin $> 9\%$); or any condition that may affect the absorption, distribution, metabolism, or excretion of the study drug.

All patients provided written informed consent. The study design was approved by the appropriate local ethical review boards and conducted in accordance with the principles of the 1996 Declaration of Helsinki of the World Medical Association.

Study design. This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study. After withdrawal of antihypertensive therapy during a 2-week washout period and a screening assessment, patients entered a 2- to 4-week single-blind placebo run-in period, at the end of which BP eligibility was confirmed and baseline BP values established.

Patients who satisfied the inclusion criteria were randomized to receive once-daily, double-blind treatment with aliskiren, 150, 300, or 600 mg, or placebo for 8 weeks. Patients were instructed to take study medication at approximately 8 AM daily, or after BP assessments on the morning of clinic visits. Patients completing the 8-week, double-blind treatment period entered a 2-week, treatment-free withdrawal period. Follow-up visits were conducted at weeks 2, 4, 6, and 8, and 4 days and 2 weeks after withdrawal.

Study objectives. The primary objective of the study was to evaluate reductions in msDBP with aliskiren 150, 300, or 600 mg compared with placebo. Secondary objectives were to assess reductions in mean sitting systolic blood pressure (msSBP); the dose-response relationship; 24-h ambulatory BP monitoring (ABPM) profiles and trough-to-peak ratios for aliskiren; the proportion of patients achieving a successful treatment response (defined as msDBP < 90 mm Hg and/or ≥ 10 mm Hg reduction from baseline) or BP control (BP $< 140/90$ mm Hg); the effects of aliskiren on PRA and RC; the safety and tolerability of aliskiren 150 to 600 mg; and the effect of treatment withdrawal on BP, PRA, and RC.

Office BP measurements. Blood pressure was measured using a standard, calibrated sphygmomanometer in accordance with the American Heart Association Committee on

Blood Pressure Determination (11). Sitting BP was measured at trough (24 ± 3 h after last dose) in the arm that gave the highest reading at the first study visit. Three BP measurements taken at 1- to 2-min intervals were used to calculate msDBP and msSBP for that visit.

Ambulatory BP monitoring. A subgroup of patients underwent 24-h ABPM before the first dose at randomization and after administration of the last dose of study medication in the double-blind treatment period. The ABPM device was calibrated to within 7 mm Hg of the mean of 3 BP measurements taken using a standard sphygmomanometer.

PRA and RC measurements. Plasma renin activity (radioimmunoassay of generated Ang I, DiaSorin kit, Saluggia, Italy) and RC (immunochemiluminescence, Nichols Direct Renin assay, San Clemente, California) were measured from plasma samples taken from a subset of patients at selected treatment centers at baseline and week 8 of the treatment period, and 4 days and 2 weeks after withdrawal in patients completing 8 weeks' treatment.

Safety and tolerability assessments. The safety population comprised all randomized patients who received at least 1 dose of study medication in the double-blind treatment period. Safety assessments included monitoring and recording all adverse events (AEs) and serious AEs (and possible relationship to study drug), laboratory tests, electrocardiograms, and vital signs. Fisher exact test was used to compare rates of individual AEs across treatment groups.

Statistical methods. A sample size sufficient for at least 138 patients per group to complete 8 weeks' treatment was selected to achieve 90% power to detect a statistically significant difference in msDBP of at least 3.5 mm Hg between aliskiren and placebo, assuming an SD of 8 mm Hg.

Efficacy analyses were performed on the intent-to-treat (ITT) population (randomized patients with efficacy measurements at baseline and at least 1 measurement in the double-blind treatment period). Analyses were performed at week 8 end point (last observation carried forward for patients discontinuing before this time).

Changes from baseline in msDBP (or msSBP) were assessed using an analysis of covariance (ANCOVA) model with treatment and region as factors and baseline msDBP (or msSBP) as a covariate. To assess the reductions in BP with aliskiren doses (150, 300, and 600 mg) compared with placebo, pairwise comparisons were performed with placebo, with Dunnett's procedure (12,13) used to adjust for the multiple comparisons of the aliskiren doses versus placebo. Changes in BP in the subgroups of Caucasian and black patients were compared by ANCOVA using the Dunnett-Hsu test to adjust for multiple comparisons.

The relationship between aliskiren dose and change from baseline in msDBP was assessed based on first-order and second-order regression analyses with dose as the predictor variable (including placebo as 0-mg dose). Linear and quadratic coefficients were tested versus 0 at the 2-sided 5% significance level. The lack-of-fit test for the model was performed at the 10% significance level.

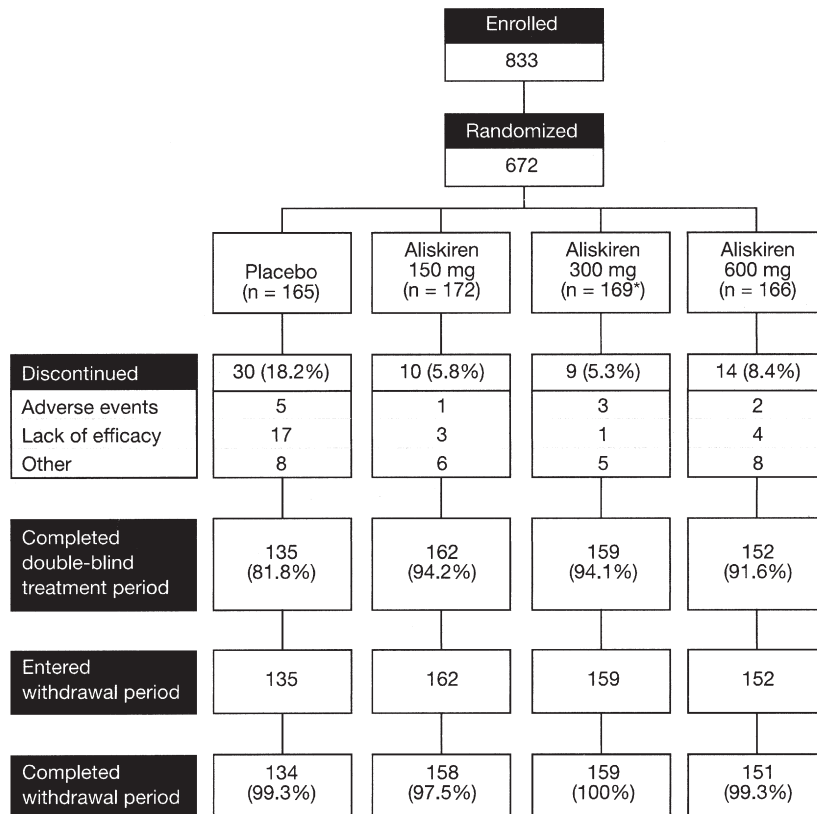


Figure 1 Patient Flow

*One patient was randomized to aliskiren 300 mg but did not have any baseline or post-baseline evaluations and was not included in numbers completing or discontinuing.

Responder and BP control rates at each aliskiren dose were compared with placebo using a logistic regression model with treatment and region as factors and baseline msDBP as a covariate.

Hourly mean ambulatory diastolic and systolic BP (maDBP and maSBP) were calculated as the mean of the readings taken during the corresponding post-dosing hour. Mean 24-h, daytime (between 6 AM and 10 PM) and nighttime (between 10 PM and 6 AM) maDBP and maSBP were also calculated.

Treatment effects on mean 24-h maDBP and maSBP were analyzed using a 2-way repeated-measures ANCOVA model with treatment, region, and post-dosing hour as factors and baseline mean 24-h maDBP and maSBP as covariates. Treatment by post-dosing-hour interaction was also included in the model. A similar ANCOVA model was used to analyze changes in mean daytime and nighttime maDBP and maSBP. Ratios between placebo-subtracted least squares mean (LSM) values at trough (post-dosing hour 24) and each of post-dosing hours 1 to 23 were calculated for each aliskiren dose. The smallest ratio was taken as the trough-to-peak ratio.

Results

Participants. Of the 833 patients enrolled in the study, 672 were randomized to double-blind treatment and comprised

the safety population. The ITT population consisted of 662 patients; of these, 608 completed 8 weeks' double-blind treatment and entered the withdrawal period (Fig. 1).

The randomized population was predominantly male (61.6%) and Caucasian (61.3%), with a mean age of 53 years. Treatment groups were well matched for demographics and baseline characteristics, although there was a slightly higher incidence of metabolic syndrome in the aliskiren 150 mg group than in other groups (Table 1).

Efficacy. Aliskiren was significantly superior to placebo in lowering msDBP and msSBP ($p < 0.0001$; ANCOVA with Dunnett's procedure to correct for multiple comparisons). Pairwise comparisons revealed that all doses (150 to 600 mg) yielded significantly greater reductions in both msDBP and msSBP than placebo (all $p < 0.0001$). After 8 weeks' treatment, aliskiren 150, 300, and 600 mg reduced msDBP by (LSM \pm SEM) 10.3 ± 0.63 , 11.1 ± 0.64 , and 12.5 ± 0.64 mm Hg, respectively, versus 4.9 ± 0.64 mm Hg with placebo.

Corresponding values for msSBP were 13.0 ± 1.01 , 14.7 ± 1.02 , and 15.8 ± 1.02 mm Hg, respectively, versus 3.8 ± 1.02 mm Hg with placebo (Fig. 2A).

Notable BP lowering (approximately 70% to 80% of maximal reductions) was apparent by week 2; maximal or near maximal reductions were achieved by week 4 and were

Table 1 Patient Demographics and Baseline Characteristics (Safety Population, n = 672)

	Placebo (n = 165)	Aliskiren			Overall (n = 672)
		150 mg (n = 172)	300 mg (n = 169)	600 mg (n = 166)	
Gender (% male)	63.0	62.2	62.7	58.4	61.6
Race (% Caucasian)	58.2	61.0	63.3	62.7	61.3
Mean age (yrs)	53	52	54	53	53
Obese (BMI ≥ 30 kg/m ²) (%)	38.8	34.9	34.9	39.8	37.1
Diabetes (%)	5.5	7.6	7.7	7.2	7.0
Metabolic syndrome* (%)	40.0	47.7	40.2	42.8	42.7
msDBP (mm Hg)	99.4	99.7	99.7	99.4	99.6
msSBP (mm Hg)	151.0	152.2	153.1	151.9	152.1
PRA† (ng/ml/h)	0.62	0.88	0.93	0.58	0.73
RC† (μ U/ml)	8.53	10.75	12.68	8.21	9.89

*Indicated by at least 3 of the following 5 features: 1) waist circumference >102 cm (men)/ >88 cm (women); 2) triglycerides ≥ 150 mg/dl or 1.69 mmol/l; 3) high-density lipoprotein cholesterol <40 mg/dl or 1.04 mmol/l (men)/ <50 mg/dl or 1.29 mmol/l (women); 4) blood pressure $\geq 130/85$ mm Hg; 5) fasting glucose ≥ 110 mg/dl or 6.1 mmol/l. †Geometric means (subgroup analysis; n = 264 for plasma renin activity [PRA]/265 for renin concentration [RC]).

BMI = body mass index; msDBP = mean sitting diastolic blood pressure; msSBP = mean sitting systolic blood pressure.

sustained throughout the remainder of the 8-week treatment period (Fig. 2B). Although aliskiren reduced msDBP to a greater extent with increasing dosage, the increase in the magnitude of effect was shallow, and the dose-response relationship was not consistent with either a linear or quadratic model ($p < 0.05$ for lack-of-fit).

The proportion of patients achieving a successful treatment response with aliskiren was significantly higher than placebo ($p < 0.0001$) for all 3 doses (59.3%, 63.3%, and 69.3%, with aliskiren 150, 300, and 600 mg, respectively, vs. 36.2% with placebo). Blood pressure control rates (BP $<140/90$ mm Hg) were also significantly higher ($p < 0.001$) with aliskiren 150, 300, and 600 mg (35.9%, 41.6%, and 46.4%, respectively) than with placebo (20.3%).

The magnitude of BP reductions with aliskiren treatment was significantly smaller in black patients (n = 79) relative to Caucasian patients (n = 408) for both msDBP ($p < 0.0001$) and msSBP ($p = 0.0004$). Least-squares mean BP reductions (SBP/DBP) at end point with aliskiren 150, 300, and 600 mg were 13.1/11.6, 13.9/11.2, and 14.7/12.5 mm Hg, respectively, in Caucasians (placebo 1.6/5.5 mm Hg) compared with 8.5/4.8, 11.2/7.5, and 9.6/8.4 mm Hg, respectively, in black patients (placebo 1.5/2.8 mm Hg).

Withdrawal effect on BP. A total of 608 patients completed 8 weeks' treatment and were eligible to enter the withdrawal period. No rebound increase in BP occurred after cessation of treatment. Blood pressure increased only gradually during the 2-week withdrawal period and did not return to baseline (Fig. 2B); msDBP remained 6.8, 6.9, and 8.7 mm Hg below baseline, and msSBP 7.9, 7.1, and 10.0 mm Hg below baseline 2 weeks after stopping aliskiren 150, 300, and 600 mg, respectively. Blood pressure remained lower in aliskiren groups than the placebo group, in which msDBP and msSBP were 5.3 and 4.9 mm Hg below baseline, respectively, at the end of the withdrawal period (Fig. 2B).

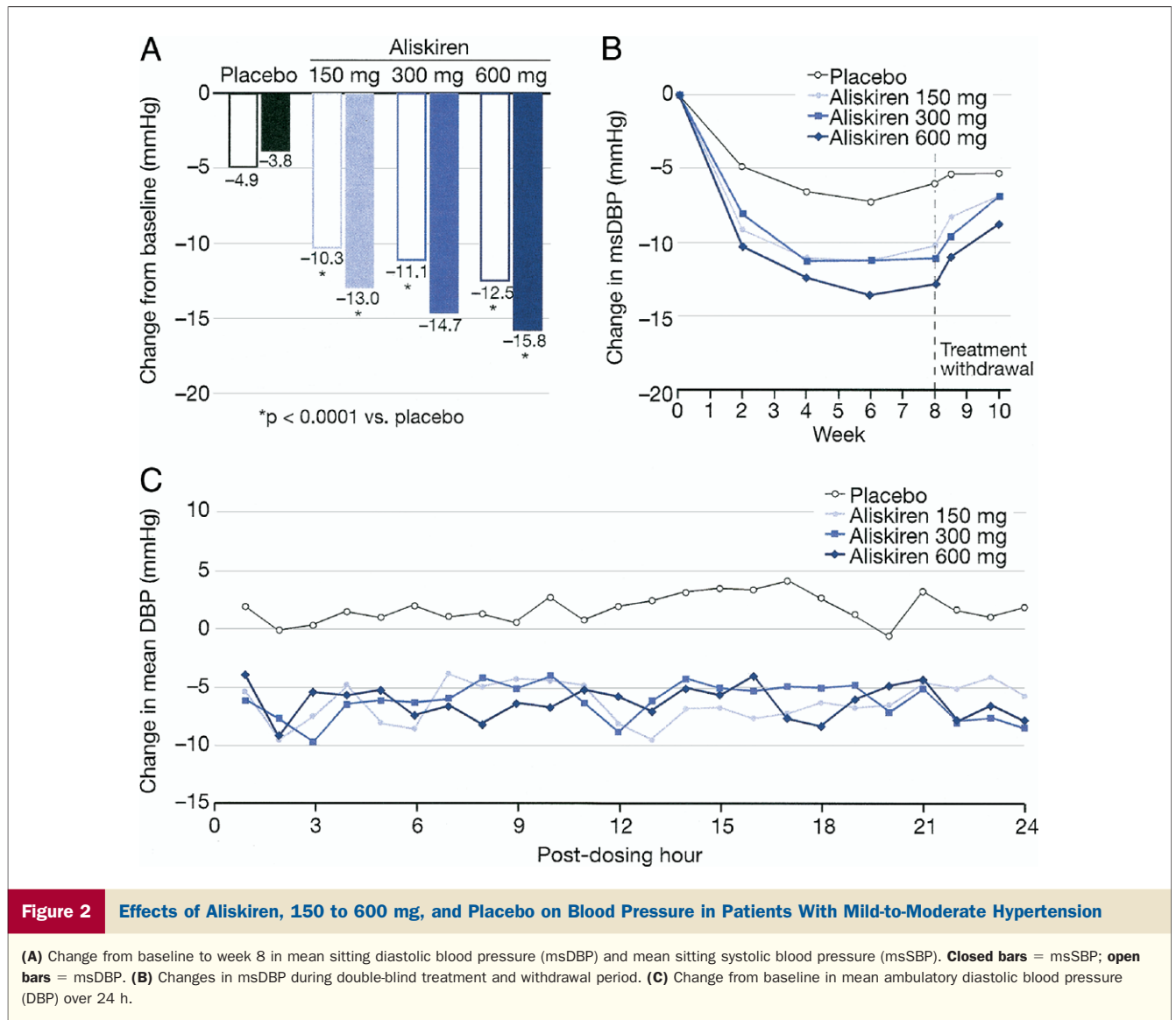
24-h ABPM. In the subgroup of 216 patients who underwent ABPM, aliskiren 150, 300, and 600 mg significantly

($p < 0.0001$) reduced mean 24-h maDBP relative to placebo by 8.16 ± 0.92 , 7.56 ± 0.90 , and 9.04 ± 0.91 mm Hg, respectively (placebo-subtracted reductions) (Fig. 2C). Similarly, significant ($p < 0.0001$ vs. placebo) reductions in 24-h maSBP were observed for aliskiren 150 (11.39 ± 1.31 mm Hg), 300 (10.52 ± 1.29 mm Hg), and 600 mg (11.67 ± 1.29 mm Hg).

Significant reductions in ambulatory BP with aliskiren versus placebo were apparent during both daytime and nighttime. Mean daytime maDBP was reduced by 6.55 ± 1.16 , 6.24 ± 1.13 , and 8.16 ± 1.14 mm Hg from baseline with aliskiren 150, 300, and 600 mg, respectively (all $p < 0.0001$ compared with an increase of 1.25 ± 1.16 mm Hg in the placebo group). Corresponding reductions in mean nighttime maDBP were 6.94 ± 1.16 , 4.77 ± 1.14 , and 6.31 ± 1.14 mm Hg with aliskiren 150, 300, and 600 mg, respectively (all $p < 0.0001$ vs. an increase of 2.16 ± 1.16 mm Hg in the placebo group). Similarly, all doses of aliskiren significantly reduced daytime and nighttime maSBP (all $p < 0.0001$ vs. placebo).

Reductions in maDBP and maSBP were consistent across the 24-h dosing interval with all aliskiren doses. Even toward the end of the dosing period, consistent maDBP lowering versus baseline and clear separation between each aliskiren dose and placebo were maintained (Fig. 2C). The trough-to-peak ratios for aliskiren 150, 300, and 600 mg were 0.64, 0.98, and 0.86, respectively.

PRA and RC. Plasma renin activity and RC measurements at baseline and week 8 of double-blind treatment were available for a subset of approximately 270 patients. Aliskiren 150, 300, and 600 mg reduced PRA from baseline (geometric mean change) by 79.5%, 81.1%, and 75.0%, respectively, whereas PRA increased by 19.5% from baseline in the placebo group. In patients entering the withdrawal period (n = 240), PRA increased gradually after withdrawal of aliskiren, but had not returned to baseline after 2 weeks; PRA remained 49.6%, 64.7%, and



63.0% below baseline in the aliskiren 150, 300, and 600 mg groups, respectively.

The 8 weeks' aliskiren treatment resulted in dose-dependent increases from baseline in RC (51.5%, 101.6%, and 228.5% for 150, 300, and 600 mg, respectively), while RC was almost unchanged in the placebo group. Renin concentration gradually returned toward baseline after withdrawal of aliskiren, but remained somewhat elevated 2 weeks after treatment discontinuation, particularly in patients who had received aliskiren 600 mg for 8 weeks (8.6%, 14.3%, and 72.9% above baseline for aliskiren 150, 300, and 600 mg groups, respectively).

Safety and tolerability. Aliskiren (150 to 600 mg) was well tolerated. During the double-blind treatment period, the proportion of patients experiencing AEs with aliskiren 150, 300, and 600 mg was 40.1%, 46.7%, and 52.4%, respectively, compared with 43.0% in the placebo group (Table 2).

The most frequent AEs overall were headache (5.4% to 9.7% across treatment groups) and nasopharyngitis (1.8% to 6.1%) (Table 2). The slightly higher overall AE rate in the aliskiren 600 mg group was largely accounted for by a significantly higher incidence of diarrhea compared with other groups (11.4% vs. 1.2% to 1.8%; $p < 0.0001$) (Table 2). However, only 1 patient in this group discontinued due to diarrhea. Overall, there were few discontinuations due to AEs, and the frequency was lower in the active treatment groups (0.6% to 1.8%) than with placebo (3.6%).

There were 4 serious AEs (1, 2, and 1 in the aliskiren 150, 300, and 600 mg groups, respectively), but none were suspected to be treatment related. No deaths occurred during the study.

During the drug withdrawal period, the most frequent AEs were headache (3.0%) and nasopharyngitis (1.2%). No patients in any of the aliskiren treatment groups had an AE involving elevated BP during this period. One patient

Table 2 Overall Incidence of AEs, Discontinuations Due to AEs, and AEs Occurring in $\geq 2\%$ of Patients During the Double-Blind Treatment Period (Safety Population, n = 672)

	Placebo (n = 165)	Aliskiren		
		150 mg (n = 172)	300 mg (n = 169)	600 mg (n = 166)
All-cause AEs	43.0	40.1	46.7	52.4
Treatment-related AEs	7.3	2.3	9.5	12.0
Discontinuation due to AEs	3.6	0.6	1.8	1.2
All-cause AEs occurring in $\geq 2\%$ of patients in any group				
Headache	9.7	7.0	7.7	5.4
Nasopharyngitis	6.1	2.9	3.6	1.8
Diarrhea	1.2	1.2	1.8	11.4*
Upper respiratory tract infection	4.2	2.3	2.4	3.0
Back pain	2.4	1.2	0.0	0.6
Dizziness	4.2	1.2	5.3	3.0
Nausea	2.4	1.2	1.8	0.0
Epistaxis	0.6	0.6	0.0	2.4
Constipation	0.6	0.0	0.0	3.6
Fatigue	0.6	0.0	1.2	3.0

Data are presented as the percentage of patients with at least 1 adverse event (AE) in the respective category. *p < 0.0001 versus other treatment groups.

(0.6%) had a serious AE (venous occlusion) during the withdrawal period.

Discussion

This study demonstrated the antihypertensive efficacy of once-daily aliskiren 150 to 600 mg in patients with mild-to-moderate hypertension, with BP reductions maintained throughout the 24-h dosing period. Overall, the BP reductions observed in this study were related to the dose of aliskiren, although the dose-response relationship was shallow. A shallow dose-response is also generally observed with angiotensin-converting enzyme inhibitors and ARBs, and has been attributed to inter-patient variability in responses to renin system inhibition (14). It should be noted, however, that studies with ARBs have shown considerable differences in the dose-response relationship among individual drugs of that class (15).

A high proportion of patients achieved a successful treatment response with aliskiren (approximately 60% to 70% across the dose range). Treatment response was defined as a reduction of msDBP from baseline to <90 mm Hg (i.e., goal attainment) or by ≥ 10 mm Hg. A 10-mm Hg difference in usual BP has been shown to be associated with at least a 2-fold difference in the rate of death from stroke, and from ischemic heart disease and other vascular causes (16). More than a third of patients achieved BP control (BP <140/90 mm Hg) at the lowest dose and 46% achieved BP control at a dose of 600 mg/day.

In this study, the 600-mg dose of aliskiren caused numerically larger BP reductions compared with the 300-mg dose (between-treatment difference in SBP/DBP 1.1/1.4 mm Hg), but the differences were not statistically significant. A previous dose-finding study by Gradman et al.

(7), which to date is the only other study to investigate the effects of aliskiren 600 mg in patients with hypertension, showed that aliskiren 300 mg provided virtually the same BP reduction as aliskiren 600 mg. The balance of evidence, therefore, suggests that aliskiren 600 mg does not offer a significantly greater BP-lowering effect than aliskiren 300 mg in patients with mild-to-moderate hypertension. The magnitude of BP reductions with aliskiren was smaller in the subset of black patients as compared with Caucasian patients in the present study, although the direction and pattern of responses were similar in the 2 racial groups. These results are consistent with the well-documented finding that the antihypertensive efficacy of renin system blockade is lower in black patients than in white patients (17,18).

Continuous, smooth BP lowering is important to maximize the benefits of antihypertensive treatment and prevent the detrimental effects of variability of ambulatory BP (19). Furthermore, most individuals experience a surge in BP in the early hours of the morning (20), the time when protection is extremely important (21,22). In the present study, aliskiren provided effective, smooth 24-h BP control, with a trough-to-peak ratio for maDBP of 64% for the 150-mg dose and in the range of 90% for higher doses. This surpasses the trough-to-peak ratios of some commonly used antihypertensive drugs (23). Consistent with its long half-life, BP suppression with aliskiren administered at approximately 8 AM was maintained throughout the high-risk period in the early hours of the following morning.

Aliskiren suppressed PRA, consistent with findings of previous studies (9,24). Although RC was increased during aliskiren treatment, due to loss of feedback inhibition by angiotensin II on renin release, potent renin

inhibition by aliskiren maintained PRA at a level substantially below baseline.

A notable degree of BP reduction was maintained for at least 2 weeks after treatment withdrawal, with no evidence of rebound effects on BP, which can be a problem with some antihypertensive drugs (25,26). Sustained BP lowering coincided with persistent PRA suppression. Sustained renin system suppression and BP lowering may be clinically beneficial, ensuring that BP control is maintained in those instances when patients inadvertently miss a dose.

Aliskiren treatment was well tolerated, the incidence of AEs being comparable with placebo at doses of 300 mg and below. The placebo-like tolerability of aliskiren at doses up to and including 300 mg is consistent with the findings of Gradman et al. (7). An increased incidence of diarrhea was seen with the highest dose of aliskiren (600 mg); the mechanism by which diarrhea was induced is not clear, and it did not occur with aliskiren 150 and 300 mg. This did not affect persistence on study treatment; few patients discontinued from the treatment period due to any AE. Due to the minimal incremental BP reduction and increased incidence of diarrhea with the 600-mg dose relative to the 300-mg dose, the clinical dose range for aliskiren for the treatment of hypertension is expected to include only the 150 and 300 mg doses.

Conclusions

This study found that aliskiren, 150 to 600 mg once daily, provides significant antihypertensive efficacy in patients with mild-to-moderate hypertension. Dosages up to and including 300 mg had placebo-like tolerability; the 600-mg dose raised no safety concerns, but was associated with diarrhea in about 11% of patients. Blood pressure reduction was sustained throughout the 24-h dosing period. Blood pressure-lowering effects gradually diminished after treatment withdrawal, but did not return to baseline by the end of 2 weeks.

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