Renin inhibition with aliskiren provides additive antihypertensive efficacy when used in combination with hydrochlorothiazide

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Objectives **Aliskiren is a novel, orally active renin inhibitor. Its antihypertensive efficacy and safety, alone and in combination with hydrochlorothiazide (HCTZ), were investigated in an 8-week, double-blind, placebo-controlled trial in hypertensive patients. The effects of these treatments on plasma renin activity (PRA) were also assessed.**

Methods **A total of 2776 patients aged ≥18 years with mean sitting diastolic blood pressure (MSDBP) 95–109 mmHg were randomized to receive once-daily treatment with aliskiren (75, 150 or 300 mg), HCTZ (6.25, 12.5 or 25 mg), the combination of aliskiren and HCTZ, or placebo, in a factorial design. The primary endpoint was the change in MSDBP from baseline to week 8. PRA was assessed at these timepoints at selected study centers.**

Results **Aliskiren monotherapy was superior to placebo ($P<0.001$; overall Dunnett's test) in reducing MSDBP and mean sitting systolic blood pressure (MSSBP). Combination treatment was superior to both component monotherapies in reducing BP (maximum MSSBP/MSDBP reduction of 21.2/14.3 mmHg from baseline with aliskiren/HCTZ 300/25 mg), and resulted in more responders (patients with MSDBP <90 mmHg and/or ≥10 mmHg reduction) and better control rates (patients achieving MSSBP/MSDBP <140/90 mmHg) than either monotherapy. Aliskiren monotherapy reduced PRA by up to 65% from baseline. Although HCTZ monotherapy increased PRA by up to 72%, PRA decreased in all of the combination therapy groups. All active treatments were well tolerated.**

Conclusions **Aliskiren monotherapy demonstrated significant BP lowering, and its effect was considerably greater when combined with HCTZ. Renin inhibition with aliskiren neutralized the compensatory rise in PRA induced by HCTZ. *J Hypertens* 25:217–226 © 2007 Lippincott Williams & Wilkins.**

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Introduction

Hypertension is a highly prevalent condition, estimated to affect over 25% of the adult population worldwide in 2000, and is a major cause of cardiovascular disease and stroke [1,2]. With the aging of the population, the incidence of hypertension is projected to rise by approximately 60% by 2025 [1].

Hypertension is a treatable disease, but despite the availability of numerous pharmacological treatment options, at least two-thirds of hypertensive patients do not have their blood pressure (BP) controlled to recommended target levels and therefore remain at increased risk of morbidity associated with high BP [3,4]. Most patients require combination therapy to reach target BP levels; fewer than 50% reach their BP goal on monotherapy [4]. Combination treatment regimens can improve BP lowering by utilizing agents from different classes with complementary mechanisms of action. A common strategy is to combine diuretics with agents that inhibit the renin–angiotensin–aldosterone system (renin system) [5–8]. The renin system plays a key role in the regulation of BP and body fluid volume homeostasis.

There are several types of diuretic, of which the thiazide diuretics, such as hydrochlorothiazide (HCTZ), are the most commonly prescribed to treat hypertension. JNC7 guidelines recommend thiazide diuretics as first-line therapy, although the guidelines also recognize that at least one additional agent is likely to be required to control BP in most patients, and recommend starting treatment with combination therapy (usually a thiazide diuretic and an agent from a different class) in patients with BP >160/100 mmHg [4]. Thiazide diuretics act at the distal tubule of the nephron to block Na^+ reuptake, thus reducing water retention and depleting fluid volume. While this effectively reduces BP,

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volume depletion stimulates release of renin from the kidney, thus increasing plasma renin activity (PRA) [9].

The resulting compensatory activation of the renin system may limit the antihypertensive benefits of diuretics. For this reason, drugs that inhibit the renin system are considered attractive candidates for combination with thiazide diuretics [10,11]. In addition, with the exception of potassium-sparing diuretics, diuretic-induced renin system activation can lead to hypokalemia, as potassium re-absorption is reduced as a consequence of increased angiotensin II-mediated aldosterone release. Renin system suppression opposes this adverse effect of thiazide diuretic use [12].

Three classes of agents that act on the renin system are currently available – angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and aldosterone receptor antagonists. As well as complementing the antihypertensive actions of diuretics, these agents are effective as monotherapy, providing substantial BP reduction and end-organ protection [13–15].

A novel, orally effective renin inhibitor, aliskiren, which targets the renin system at its point of activation, is now under investigation. Aliskiren is a potent inhibitor of human renin [16], with a half-life of approximately 40 h [17], making it suitable for once-daily dosing. Unlike ACE inhibitors and ARBs, aliskiren provides suppression of the renin system without inducing reactive rises in PRA. Aliskiren monotherapy has demonstrated antihypertensive efficacy in short-term studies in patients with mild-to-moderate hypertension, providing double-digit reductions in BP [18–21]. Aliskiren 150 mg showed comparable efficacy to the ARBs irbesartan 150 mg [18] and losartan 100 mg [20] in reducing BP, and in patients with type 1 or 2 diabetes and mild-to-moderate hypertension, aliskiren 300 mg produced similar BP reductions to the ACE inhibitor, ramipril 10 mg [21]. Aliskiren treatment was well tolerated in these studies, showing placebo-like tolerability at doses up to 300 mg [18,19]. In addition, aliskiren 150 mg in combination with HCTZ 25 mg has shown additional BP lowering compared with aliskiren 150 mg alone in patients with hypertension in a small open-label pilot study [22]. The aim of the current study was to provide a comprehensive assessment of the efficacy, safety and tolerability of aliskiren in combination with HCTZ at a range of doses.

Here we report the antihypertensive efficacy of aliskiren both as monotherapy and in combination with HCTZ in patients with mild-to-moderate essential (primary) hypertension. In addition to measuring antihypertensive effects, PRA and renin concentration (RC) were assessed.

Methods

Study population

Men and women aged 18 years or older with mild-to-moderate essential hypertension [mean sitting diastolic BP (MSDBP) ≥ 95 and < 110 mmHg at baseline] were recruited at 213 centers worldwide. Exclusion criteria included pregnancy or breastfeeding, severe hypertension [MSDBP ≥ 110 mmHg and/or mean sitting systolic BP (MSSBP) ≥ 180 mmHg], history or evidence of secondary hypertension, type 1 or type 2 diabetes mellitus with poor glycemic control [glycosylated hemoglobin (HbA_{1c}) $\geq 9\%$], or any surgical or medical condition that might significantly alter the absorption, distribution, metabolism or excretion of study drugs. All patients provided written informed consent. The study protocol was approved by the appropriate local ethical review boards and the study was conducted in accordance with the principles of the Declaration of Helsinki (1996) of the World Medical Association.

Study design

This was an 8-week, multicenter, randomized, double-blind, placebo-controlled, multifactorial, parallel-group trial.

After withdrawal of existing antihypertensive therapy during a 1-week washout period, patients entered a single-blind, placebo run-in period. Eligibility of MSDBP ≥ 95 mmHg was assessed after 2 weeks on placebo; patients who failed to meet inclusion criteria underwent an additional 2 weeks' placebo run-in and were re-assessed for eligibility.

Eligible patients were randomized to receive double-blind treatment with placebo, aliskiren monotherapy (75, 150 or 300 mg), HCTZ monotherapy (6.25, 12.5 or 25 mg), or a combination of aliskiren and HCTZ (every dose combination except aliskiren/HCTZ 300/6.25 mg) in a factorial design. Extra aliskiren/HCTZ dose combinations were included in addition to the low/low, medium/medium, and high/high combinations that form the basis of multifactorial studies, to provide a more comprehensive assessment of the treatment combinations most likely to be used in clinical practice (i.e. aliskiren/HCTZ 150/12.5 mg, 150/25 mg, 300/12.5 mg and 300/25 mg). Patients randomized to HCTZ 25 mg combined with aliskiren 150 or 300 mg received double-blind treatment with aliskiren/HCTZ 150/12.5 mg for 1 week before forced titration to their assigned treatment. Double-blind treatment was administered once daily for 8 weeks.

Study objectives

The co-primary objectives of this study were: to compare the effect of once-daily aliskiren 75, 150 or 300 mg with that of placebo on the change from baseline in MSDBP; and to compare the effects of aliskiren/HCTZ

combinations with those of their component monotherapies on change from baseline in MSDBP. As secondary objectives, the same comparisons were also made for the change from baseline in MSSBP.

Secondary objectives also included assessment of the dose–response efficacy for all treatment groups; the proportion of patients showing a successful response to therapy (MSDBP <90 mmHg and/or ≥ 10 mmHg reduction from baseline); the proportion of patients achieving BP control (MSDBP <90 mmHg and MSSBP <140 mmHg); the safety and tolerability of aliskiren alone and in combination with HCTZ; and the effects of treatment on PRA and RC.

Clinic BP and heart rate measurement

BP measurements were performed at baseline and weeks 1, 2, 4, 6 and 8 of the 8-week double-blind treatment period. Sitting clinic BP was measured using a calibrated standard mercury sphygmomanometer [in accordance with the 1988 American Heart Association (AHA) Committee on Blood Pressure Determination] [23], or an alternative calibrated method in the event that standard mercury sphygmomanometers were not available as a result of regulation. BP was measured at trough (24 ± 3 h post dose) in the arm that recorded the highest BP measurement at the first study visit. Three seated BP measurements were made at 1–2-min intervals, from which MSDBP and MSSBP for that visit were calculated.

PRA and RC measurements

PRA and RC were assayed using plasma samples taken at baseline and week 8 in a subset of patients at selected treatment centers. PRA was measured by means of radioimmunoassay of generated angiotensin I (DiaSorin kit; DiaSorin, Stillwater, Minnesota, USA) and RC by immunochemiluminescence (Nichols Direct Renin assay; Nichols Institute, San Clemente, California, USA). These data were intended to provide a descriptive assessment of the effects of aliskiren and HCTZ, alone and in combination, on PRA and RC.

Safety and tolerability evaluations

Safety evaluations consisted of monitoring and recording all adverse events (AEs), serious adverse events (SAEs), vital signs and laboratory safety evaluations. AEs were reported voluntarily by patients or detected through physical examination or questioning of the patient by the investigator. All AEs were assessed for possible relationship to study drug, and the duration and intensity of symptoms and outcome were recorded. The safety population comprised all patients who were randomized and received at least one dose of double-blind study medication.

Statistical methods

All efficacy analyses were performed on the intent-to-treat (ITT) population (all randomized patients with a baseline measurement and at least one post-baseline measurement).

The study was powered (90%) to detect a statistically significant difference, at the two-sided 0.05 significance level, in the change from baseline in MSDBP between the aliskiren monotherapy groups and placebo, assuming a treatment difference of 3.3 mmHg and a standard deviation of 8 mmHg, using Dunnett's multiple comparison procedure. The calculated sample size of 161 completed patients per group also provided at least 90% power to detect a significant difference between the combination groups and both respective monotherapy treatments, assuming a treatment difference of 3.2 mmHg and standard deviation of 8 mmHg.

To evaluate the antihypertensive efficacy of aliskiren monotherapy compared with placebo, the changes from baseline in MSDBP and MSSBP were analyzed in two-way analysis of covariance (ANCOVA) models, with treatment group and region as factors, and the respective baseline value as covariate. The null hypothesis was no treatment difference between the three aliskiren treatment groups (75, 150 and 300 mg) and placebo. Dunnett's procedure was used to correct for multiple comparisons. Pairwise comparisons with 95% confidence intervals (CIs) were also performed between each aliskiren dose and placebo, nominal P values were generated and Dunnett's procedure was used to correct for multiple comparisons (Dunnett's adjusted P values).

To assess whether both component monotherapies contributed to the antihypertensive efficacy of the combination of aliskiren and HCTZ, the primary efficacy variable was analyzed by a two-way ANCOVA model with four-level aliskiren and four-level HCTZ treatments as the two factors and baseline MSDBP as a covariate. Pairwise comparisons between combinations and component monotherapies or placebo were based on a two-way ANCOVA, with treatment and region as factors and baseline as the covariate.

The relationship between the BP-lowering effect and the dose of each drug was examined by means of dose–response surface analyses for MSDBP and MSSBP at endpoint, with the aliskiren and HCTZ doses as predictor variables. Second-order analysis was planned to be carried out in the event of significant lack-of-fit (at a significance level of 0.1) for the first-order analysis.

Responder and control rate analyses

The proportion of patients defined as responders (MSDBP <90 mmHg and/or ≥ 10 mmHg reduction from baseline), and the proportion of patients achieving BP control (MSDBP <90 mmHg and MSSBP <140 mmHg) were analyzed using a logistic regression model with treatment and region as factors, and baseline MSDBP as covariate.

Table 1 Patient demographics and baseline characteristics (randomized population)

		Aliskiren			HCTZ			Aliskiren/HCTZ combinations							
	Placebo ($n=195$)	75 ($n=184$)	150 ($n=185$)	300 ($n=183$)	6.25 ($n=194$)	12.5 ($n=188$)	25 ($n=176$)	75/6.25 ($n=188$)	75/12.5 ($n=193$)	75/25 ($n=186$)	150/6.25 ($n=176$)	150/12.5 ($n=186$)	150/25 ($n=188$)	300/12.5 ($n=181$)	300/25 ($n=173$)
Sex (% male)	55.9	56.0	60.5	54.1	56.2	54.8	52.3	57.4	52.3	54.3	54.5	52.7	55.3	49.2	56.6
Race (%)															
Caucasian	84.1	83.2	84.9	84.7	83.0	85.1	88.1	87.8	85.5	88.7	84.7	84.9	86.7	84.5	86.1
Black	3.6	4.9	5.9	3.8	6.7	4.8	5.1	2.7	6.2	2.7	4.5	5.4	2.7	5.5	4.0
Asian	2.6	3.3	2.2	1.6	2.6	1.6	2.3	3.7	2.1	2.2	2.8	2.7	2.1	2.8	2.9
Other	9.7	8.7	7.0	9.8	7.7	8.5	4.5	5.9	6.2	6.5	8.0	7.0	8.5	7.2	6.9
Ethnicity (%)															
Hispanic/Latin	28.2	25.5	29.7	30.1	27.8	26.6	25.6	24.5	23.3	28.5	31.3	28.0	26.6	27.6	28.3
Chinese	2.6	2.7	2.2	1.6	1.0	1.6	1.7	2.1	2.1	2.2	2.3	2.2	2.1	2.2	1.7
Other	69.2	71.7	68.1	68.3	71.1	71.8	72.7	73.4	74.6	69.4	66.5	69.9	71.3	70.2	69.9
Mean age (years)	54.4	55.0	53.5	54.2	55.2	55.4	55.1	55.1	54.4	54.7	53.9	54.7	53.7	55.5	54.8
Mean duration of HTN[a] (years)	7.1	7.9	7.3	7.7	7.4	7.9	8.4	6.5	7.8	8.3	7.0	7.8	7.4	7.9	8.4
Obese (BMI $\geq 30\,kg/m^2$) (%)	40.5	41.8	32.4	38.8	41.2	38.8	32.4	37.8	39.9	38.7	37.5	35.5	37.8	42.0	41.0
Diabetic (%)[b]	8.2	8.7	6.5	7.1	9.8	4.8	8.0	7.4	9.3	7.0	8.0	5.4	7.4	6.1	10.4
Metabolic syndrome[c] (%)	38.5	33.7	35.1	35.5	33.0	38.3	35.2	39.4	33.2	37.6	31.8	33.9	38.3	34.8	35.3
Baseline MSDBP (mmHg)	99.3	99.4	98.8	99.3	99.3	99.1	99.1	98.9	100.0	99.0	99.0	99.1	98.4	99.5	99.3
Baseline MSSBP (mmHg)	152.7	153.2	153.4	154.4	153.4	153.4	154.5	154.5	154.0	152.9	153.3	154.1	153.2	153.2	154.6
Baseline PRA[d] (ng/ml per h)	0.36	0.56	0.44	0.32	0.65	0.38	0.40	0.46	0.55	0.52	0.49	0.45	0.61	0.42	0.60
Baseline RC[d] (μU/ml)	12.8	16.4	14.1	10.7	19.6	14.7	10.7	14.3	14.7	15.8	16.2	14.8	17.0	13.6	16.9

HCTZ, hydrochlorothiazide; HTN, hypertension; BMI, body mass index; MSDBP, mean sitting diastolic blood pressure; MSSBP, mean sitting systolic blood pressure; PRA, plasma renin activity; RC, renin concentration. All dosages are shown in milligrams. [a] Naïve patients are not included. [b] Includes both type 1 and type 2 diabetes. [c] At least three of the following features: waist circumference >102 cm (men)/>88 cm (women); triglycerides ≥150 mg/dl or 1.69 mmol/l; high-density lipoprotein (HDL) cholesterol < 40 mg/dl or 1.04 mmol/l (men), or < 50 mg/dl or 1.29 mmol/l (women); BP ≥ 130/85 mmHg; fasting glucose ≥ 110 mg/dl or 6.1 mmol/l. [d] Geometric mean for patients with both baseline and post-baseline measurements. The randomized population comprised all patients who received a randomization number, regardless of whether they received double-blind medication.

Results

Study population, demographics and baseline characteristics

A total of 3190 patients were enrolled in the study, of whom 2776 met eligibility criteria and were randomized to receive double-blind treatment. Demographics and baseline characteristics were similar across treatment groups (Table 1). The ITT population comprised a total of 2752 patients, and 2762 patients were included in safety analyses. The subset of patients in which PRA and RC were assessed included 34–47 patients per treatment group.

Efficacy

Primary efficacy endpoints

Aliskiren monotherapy was significantly superior to placebo in reducing MSDBP ($P = 0.0002$; overall Dunnett's test). Aliskiren reduced MSDBP in a dose-related manner. Least squares mean (LSM) ± standard error reductions from baseline were 8.7 ± 0.59, 8.9 ± 0.59 and 10.3 ± 0.60 mmHg at doses of 75, 150 and 300 mg, respectively (Fig. 1). Pairwise comparisons showed that all three doses of aliskiren were statistically superior to placebo based on the nominal P values; however, the Dunnett's-adjusted P values indicated that while aliskiren 150 mg and 300 mg were significantly superior to placebo, the 75 mg dose was not ($P = 0.09$). HCTZ monotherapy reduced MSDBP from baseline, although no linear dose relationship was observed (LSM reductions of 9.1 ± 0.58, 10.1 ± 0.59 and 9.4 ± 0.61 mmHg at doses of 6.25, 12.5 and 25 mg, respectively; all nominal P values were <0.01 versus placebo) (Fig. 1).

The overall test for combination therapy revealed that both aliskiren and HCTZ made statistically significant contributions to the reductions in MSDBP from baseline at endpoint ($P < 0.0001$). All combinations were superior to placebo ($P < 0.0001$), and most were superior to both monotherapies (exceptions were aliskiren/HCTZ 150/6.25 mg versus either monotherapy and aliskiren/HCTZ 75/12.5 versus HCTZ monotherapy; Fig. 1). Reductions (LSM ± standard error) in MSDBP from baseline to endpoint with combination therapy ranged from 10.4 ± 0.59 to 14.3 ± 0.61 mmHg.

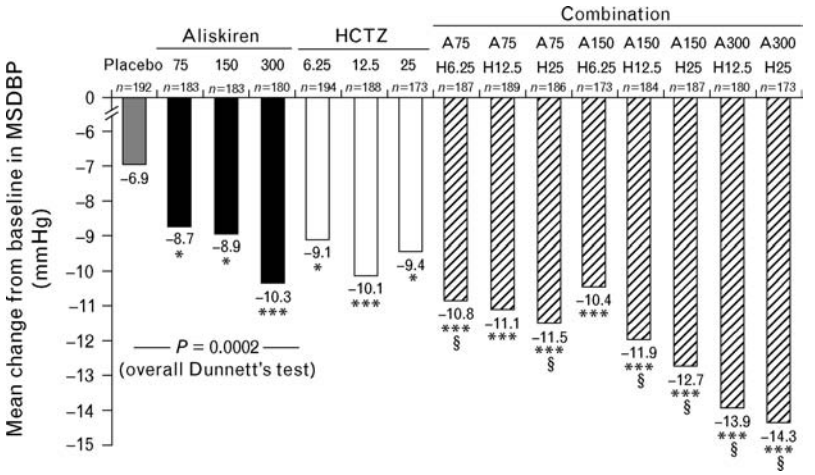
Secondary efficacy endpoints

Aliskiren significantly reduced MSSBP from baseline compared with placebo ($P < 0.0001$; overall Dunnett's test). Doses of 150 and 300 mg were significantly superior to placebo ($P < 0.0001$; nominal and Dunnett's adjusted values), but the 75 mg dose was not (nominal P value = 0.151; Dunnett's adjusted P value = 0.343) (Fig. 2).

Combination treatment was consistently superior to component monotherapies in reducing MSSBP from baseline ($P < 0.05$), with the exception of aliskiren/HCTZ 75/12.5 mg versus HCTZ monotherapy (Fig. 2). Reductions (LSM ± standard error) in MSSBP from baseline to endpoint with combination therapy ranged from 14.3 ± 0.93 to 21.2 ± 0.97 mmHg (Fig. 2).

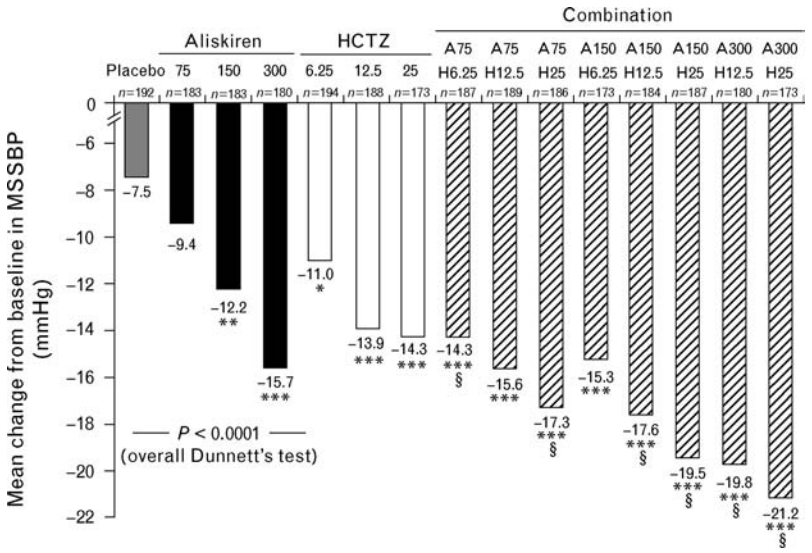
The dose–response surface analyses of MSDBP and MSSBP were fitted in the second order, and indicated that BP reductions were related to the doses of both aliskiren and HCTZ. The fitted predicted values were consistent with the raw means, with the greatest BP reductions being observed in the aliskiren/HCTZ 300/25 mg group (raw mean reductions of 21.5/14.3 mmHg for MSSBP/MSDBP).

Fig. 1



Least squares mean change from baseline to week 8 in mean sitting diastolic blood pressure (MSDBP) with aliskiren (A) and hydrochlorothiazide (HCTZ; H) monotherapy and combination therapy (intent-to-treat population). Dosages in milligrams. $*P < 0.05$; $**P < 0.001$; $***P \leq 0.0001$ versus placebo; $^{\S}P < 0.05$ versus each component monotherapy (nominal P values for pairwise comparisons).

Fig. 2

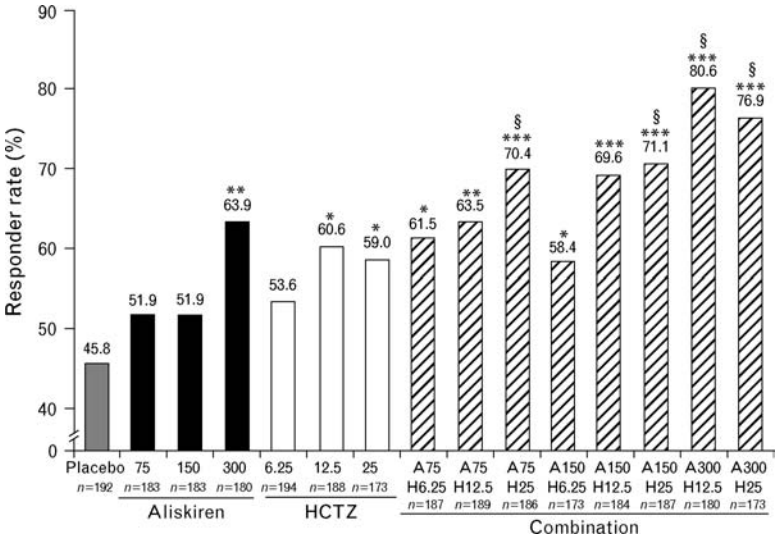


Least squares mean change from baseline to week 8 in mean sitting systolic blood pressure (MSSBP) with aliskiren (A) and hydrochlorothiazide (HCTZ; H) monotherapy and combination therapy (intent-to-treat population). Dosages in milligrams. $*P < 0.05$; $**P < 0.001$; $***P \leq 0.0001$ versus placebo; $^{\S}P < 0.05$ versus each component monotherapy (nominal P values for pairwise comparisons).

Responder rates were significantly higher with aliskiren 300 mg (63.9%; $P = 0.0005$), HCTZ 12.5 and 25 mg (60.6 and 59.0%, respectively; both $P < 0.02$) and all combination doses (58.4–80.6%; all $P < 0.05$) than placebo (45.8%). Responder rates for all combinations of aliskiren (75–300 mg) with HCTZ 25 mg and aliskiren/HCTZ 300/12.5 mg were superior to both monotherapies ($P < 0.05$), while aliskiren/HCTZ 75/12.5 and 150/12.5 mg were superior to their respective aliskiren monotherapies ($P < 0.05$) (Fig. 3).

There was a trend towards improved control rates (proportion of patients with MSDBP < 90 mmHg and MSSBP < 140 mmHg at study end) with combination therapy (37.4–59.5%) compared with either aliskiren monotherapy (29.0–46.7%) or HCTZ monotherapy (32.5–37.8%).

Fig. 3



Responder rates (% of patients with mean sitting diastolic blood pressure < 90 mmHg and/or ≥ 10 mmHg decrease from baseline) with aliskiren (A) and hydrochlorothiazide (HCTZ; H) monotherapy and combination therapy (intent-to-treat population). Dosages in milligrams. $*P < 0.05$; $**P < 0.001$; $***P \leq 0.0001$ versus placebo; $^{\S}P < 0.05$ versus each component monotherapy.

In the monotherapy groups, only aliskiren 300 mg led to statistically significantly greater control rates than placebo (46.7 versus 28.1%; $P = 0.0001$); control rates were not statistically significantly higher than placebo with any HCTZ dose. However, with all combinations, except the lowest doses of each drug (aliskiren/HCTZ 75/6.25 mg), control rates were superior to placebo (all $P < 0.02$). Combinations utilizing the higher doses of one or both drugs (aliskiren 75–300 mg with HCTZ 25 mg or aliskiren 150–300 mg with HCTZ 12.5 mg) yielded control rates that were statistically superior to each component monotherapy.

PRA and RC

Patients receiving aliskiren 75, 150 and 300 mg monotherapy had decreases in PRA from baseline of 54.2, 65.1 and 57.6% (geometric means), respectively. In contrast, PRA increased by 3.5, 44.7 and 71.9% with HCTZ 6.25, 12.5 and 25 mg, respectively. However, when HCTZ was combined with aliskiren, decreases in PRA of 46.1–63.5% were observed. PRA was unchanged in the placebo group (0.7% increase from baseline) (Fig. 4).

A dose-related increase in RC from baseline was observed with increasing dose of aliskiren monotherapy (164, 192 and 348% with aliskiren 75, 150 and 300 mg, respectively). The highest HCTZ dose, 25 mg, also increased RC, although to a lesser extent (108% increase). Lower doses of HCTZ did not increase RC relative to placebo (10, 26 and 30% increases from baseline, with HCTZ 6.25 and 12.5 mg, and placebo, respectively). RC increased in all combination groups; the magnitude of increase was related to dosages of both drugs, with the most marked increase (1211% from baseline) occurring in the aliskiren/HCTZ 300/25 mg group. Increases in RC in several combination groups were considerably greater than the sum of the increases seen with each component.

Safety

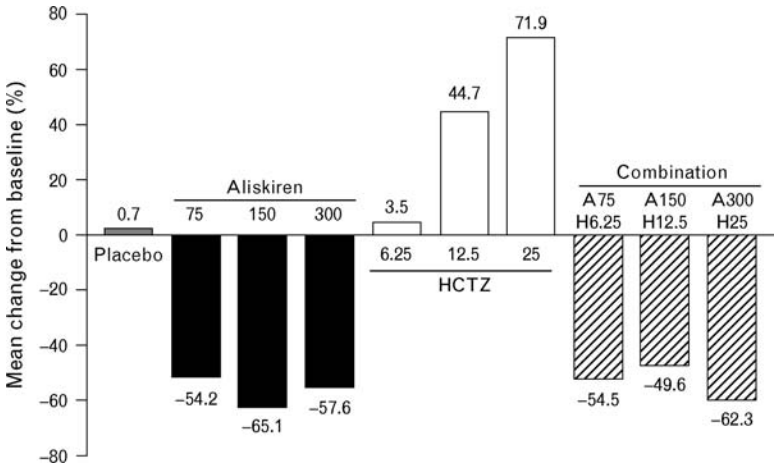
All active treatments were well tolerated, with the overall proportion of patients experiencing AEs falling in the range 37.3–39.2% with aliskiren monotherapy, 38.7–42.0% with HCTZ monotherapy, and 34.6–45.3% with aliskiren/HCTZ combination (no dose relationship was observed), while 44% of placebo recipients experienced AEs (Table 2). Few patients discontinued as a result of AEs (0–4.4%; Table 2).

The most frequent AEs overall were headache (7.2%) and nasopharyngitis (3.8%) (Table 2). There were few severe AEs (0.5–3.9%) or SAEs (0–2.6%); one death occurred in the aliskiren/HCTZ 150/25 mg group (due to thoracic trauma from a traffic accident), but this was not considered to be related to the study medication.

Only a small proportion of patients (10.7%) experienced AEs that were suspected by investigators to be related to the study drug (compared with 40.2% of patients experiencing AEs overall). The overall incidence of suspected treatment-related AEs appeared slightly higher in the HCTZ (9.3–11.0%) and combination groups (8.7–16.6%) compared with placebo (8.8%) and aliskiren (6.5–9.8%) groups (Table 2). However, this could not be attributed to any particular AE or class of AE.

Hypokalemia (serum potassium below the normal limit, i.e. < 3.5 mmol/l) occurred with the highest frequency in HCTZ 12.5 and 25 mg groups (3.9 and 5.2%, respectively). When these doses of HCTZ were administered in combination with aliskiren, the frequency of hypokalemia dropped to 0.7–2.0% for the combination groups

Fig. 4



Change from baseline (geometric mean %) in plasma renin activity with aliskiren (A) and hydrochlorothiazide (HCTZ; H) monotherapy and selected combinations (intent-to-treat population subset). Dosages in milligrams.

Table 2 Overall incidence of adverse events (AEs), discontinuations due to AEs, AEs occurring in ≥5% of patients, and selected abnormal laboratory results (safety population; monotherapy and combination therapy)

		Aliskiren			HCTZ			Aliskiren/HCTZ combinations							
	Placebo	75	150	300	6.25	12.5	25	75/6.25	75/12.5	75/25	150/6.25	150/12.5	150/25	300/12.5	300/25
All-cause AEs (% of patients)	44.0	37.5	37.3	39.2	38.7	42.0	41.6	34.6	39.5	41.4	37.9	39.1	44.1	45.3	41.0
Treatment-related AEs (% of patients)	8.8	9.8	6.5	7.2	9.3	10.1	11.0	10.1	14.2	9.1	10.9	8.7	16.0	16.6	12.1
Discontinuation due to AEs (% of patients)	3.6	0.5	0	4.4	1.0	0.5	2.3	1.6	3.7	2.2	4.0	2.2	3.2	1.7	2.9
All-cause AEs occurring in ≥5% of patients in any group (% of patients)															
Headache	13.5	7.1	7.0	5.5	6.2	8.0	6.9	5.9	7.4	5.9	4.6	8.2	4.8	8.8	8.1
Nasopharyngitis	5.2	4.9	2.7	1.7	3.1	4.8	3.5	4.8	3.2	5.4	2.9	1.6	3.7	3.9	5.2
Selected abnormal laboratory results (% of patients)															
Hypokalemia ($K^+ < 3.5$ mmol/l)	1.3	0	0	1.5	0.6	3.9	5.2	1.3	1.3	2.7	0.7	0.7	3.4	2.0	2.2

HCTZ, hydrochlorothiazide. All dosages are shown in milligrams.

with HCTZ 12.5 mg and to 2.2–3.4% for the combination groups with HCTZ 25 mg (Table 2).

Discussion

In the current study, aliskiren monotherapy effectively reduced MSDBP and MSSBP compared with placebo in a dose-related manner in patients with mild-to-moderate hypertension, and provided significant additional BP reductions when used in combination with HCTZ. These findings are consistent with previous studies investigating the effectiveness of aliskiren monotherapy [18,20], and confirmed the efficacy of aliskiren and HCTZ in combination previously observed in a smaller uncontrolled pilot study [22]. Although the 75 and 150 mg doses of aliskiren resulted in similar reductions in MSDBP in the current study, aliskiren has demonstrated greater reductions in both MSDBP and MSSBP at the 150 mg compared with the 75 mg dose in a previous study [20]. A pooled analysis of aliskiren data from five placebo-controlled studies (including the current study) also showed consistently greater BP reductions with the 150 mg than the 75 mg dose [24]. This study demonstrates that renin inhibition with aliskiren is an effective alternative to ACE inhibitors and ARBs as add-on agents in patients who do not respond adequately to diuretic monotherapy [7,25], providing BP reductions comparable with valsartan/HCTZ combination therapy [25,26].

A high proportion of patients fail to respond adequately to antihypertensive monotherapy, leaving them at increased risk of poor outcomes [4]. Aliskiren 300 mg combined with HCTZ 12.5 mg resulted in a very high responder rate (81% of patients achieved MSDBP < 90 mmHg and/or ≥ 10 mmHg reduction), which was significantly greater than with either monotherapy. The beneficial effect of aliskiren and HCTZ in combination was also illustrated by higher control rates compared with component monotherapies. Up to 60% of patients achieved BP control on aliskiren/HCTZ combination therapy, compared with a maximum of 47% on aliskiren monotherapy and 38% on HCTZ monotherapy.

The capacity of aliskiren to enhance the antihypertensive efficacy of HCTZ reflects its complementary mode of action, targeting the renin system at its point of activation and thus suppressing PRA. In the present study, aliskiren reduced PRA by up to 65% from baseline, consistent with its mode of action and with previous findings in both healthy volunteers [27,28] and hypertensive patients [29]. As expected, HCTZ monotherapy increased PRA; however, when aliskiren and HCTZ were administered in combination, renin inhibition by aliskiren was sufficient to fully neutralize the HCTZ-induced rise in PRA, resulting in an overall decrease in PRA.

Effective inhibition of the renin system by aliskiren was reflected in dose-related increases in RC from baseline (a consequence of loss of feedback inhibition by angiotensin II). HCTZ at doses above 6.25 mg also increased RC, as a result of stimulated renin release in response to reduced intravascular volume. Combinations of aliskiren and HCTZ were associated with marked elevation of RC (up to 13-fold in the aliskiren/HCTZ 300/25 mg group), suggestive of a synergistic effect on the renin system through the complementary modes of action of the two drugs. As noted above, aliskiren effectively inhibited the renin enzyme, despite marked elevation of RC, to produce an overall reduction in PRA from baseline. This is in contrast to agents that block the renin system at other points, such as ACE inhibitors and ARBs, which induce increases in PRA in parallel with RC [27,28].

By providing direct inhibition of renin, aliskiren suppresses the renin system at the point of activation, differentiating it from agents that act at other points in the renin system. Both ACE inhibitors and ARBs interrupt the feedback regulation of renin release by angiotensin II, resulting in increased renin levels and increased PRA. Thus, neither class of agent provides optimal suppression of the renin system. The increased angiotensin I levels seen with ACE inhibitor treatment can lead to 'escape' as angiotensin I is converted to angiotensin II by

ACE-independent pathways [30]. Clinical studies have linked feedback stimulation of renin activity with escape from ACE inhibition [31,32]. Increased levels of angiotensin I and II could lead to increased levels of biologically active angiotensin fragments, although the effects of these peptides on the cardiovascular and renal systems have yet to be fully elucidated [33]. Aldosterone also has an important role in cardiovascular disease. Treatment with the selective aldosterone receptor antagonist eplerenone has been shown to reduce BP, protect against end-organ damage and improve patient outcomes [34]. ACE inhibitors and ARBs initially reduce aldosterone levels but longer-term treatment with these agents is typically associated with incomplete aldosterone suppression [35]. The effects of direct renin inhibition on aldosterone remain to be established.

Agents that inhibit renin system activity have the benefit of opposing the adverse effects of thiazide diuretics on potassium homeostasis [12]. In the present study, hypokalemia occurred at a lower rate in patients on combination therapy than in those on HCTZ alone, suggesting that adding aliskiren did reduce the risk of developing hypokalemia during diuretic treatment.

The safety profile of each drug is an important consideration with combination therapy, as compliance may be compromised if addition of a new drug exacerbates or induces adverse effects. Placebo-like tolerability of aliskiren monotherapy has been demonstrated previously [18], and was further supported in this study. HCTZ was also well tolerated, and combination of the two drugs did not increase the incidence of AEs, even at the highest doses of each.

Aliskiren represents a promising addition to the available treatment options for hypertension. This study not only confirms that aliskiren is effective as monotherapy, but also demonstrates that aliskiren provides significant additional BP lowering when used in combination with HCTZ. Further studies are now needed to determine the effects of aliskiren treatment on long-term BP control and its ability to protect against end-organ damage.

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