# Comparative efficacy and safety of aliskiren, an oral direct renin inhibitor, and ramipril in hypertension: a 6-month, randomized, double-blind trial

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***Objectives*** **This double-blind study compared long-term efficacy, safety and tolerability of the oral direct renin inhibitor aliskiren and the angiotensin-converting enzyme inhibitor ramipril alone and combined with hydrochlorothiazide in patients with hypertension.**

***Methods*** **After a 2–4-week placebo run-in, 842 patients [mean sitting diastolic blood pressure (msDBP) 95–109 mmHg] were randomized to aliskiren 150 mg ($n = 420$) or ramipril 5 mg ($n = 422$). Dose titration (to aliskiren 300 mg/ramipril 10 mg) and subsequent hydrochlorothiazide addition (12.5 mg, titrated to 25 mg if required) were permitted at weeks 6, 12, 18 and 21 for inadequate blood pressure control. Patients completing the 26-week active-controlled treatment period were re-randomized to their existing regimen or placebo for a 4-week double-blind withdrawal phase.**

***Results*** **Six hundred and eighty-seven patients (81.6%) completed the active treatment period. At week 26, aliskiren-based therapy produced greater mean reductions in mean sitting systolic blood pressure (17.9 versus 15.2 mmHg, $P = 0.0036$) and msDBP (13.2 versus 12.0 mmHg, $P = 0.025$), and higher rates of systolic blood pressure control (<140 mmHg; 72.5 versus 64.1%, $P = 0.0075$) compared with ramipril-based therapy. During withdrawal, blood pressure increased more rapidly after stopping ramipril than aliskiren-based therapy; median blood pressure reached 140/90 mmHg after 1 and 4 weeks, respectively. Blood pressure reductions were maintained with continued active treatment. Aliskiren therapy was well tolerated. Overall adverse event rates were similar with aliskiren (61.3%) and ramipril (60.4%); cough was more frequent with ramipril (9.5%) than aliskiren (4.1%).**

***Conclusions*** **Aliskiren-based therapy was well tolerated and produced sustained blood pressure reductions in patients with hypertension over 6 months, greater than those with ramipril-based therapy.** ***J Hypertens*** **26:589–599 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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**Keywords: angiotensin-converting enzyme inhibitor, aliskiren, antihypertensive therapy, direct renin inhibitor, diuretic, ramipril**

**Abbreviations: ACE, angiotensin converting enzyme; AE, adverse event; ANCOVA, analysis of covariance; Ang, angiotensin; ARB, angiotensin receptor blocker; BMI, body mass index; BUN, blood urea nitrogen; DBP, diastolic blood pressure; ECG, electrocardiogram; $HbA_{1c}$, glycosylated haemoglobin; HCTZ, hydrochlorothiazide; ITT, intent-to-treat; LOCF, last observation carried forward; msDBP, mean sitting diastolic blood pressure; msSBP, mean sitting systolic blood pressure; PRA, plasma renin activity; SAE, serious adverse event; SBP, systolic blood pressure; URTI, upper respiratory tract infection**

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## Introduction

Hypertension is a major risk factor for cardiovascular morbidity and mortality [1], and its early detection and control reduces cardiovascular events [2]. For many patients, however, blood pressure (BP) control is inadequate, and the number of individuals meeting recommended targets can be as low as 25% [3–5]. Long-term BP treatment and control is required to reduce the risk of morbidity and mortality associated with hypertension [6], which highlights the importance of good adherence and long-term persistence with therapy [3].

The renin system plays a key role in the acute and chronic regulation of BP [7]. Although angiotensin-converting enzyme (ACE) inhibitors and ARBs block the renin system by inhibiting the production or action of angiotensin (Ang) II, they result in a reactive rise in plasma renin activity (PRA) [8]. With ACE inhibitors, the increased levels of Ang I raise the possibility of 'escape' from ACE inhibition as Ang I can be converted to Ang II by ACE-independent pathways [9]. In contrast, direct renin inhibitors block the renin system at its point of

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activation, and therefore represent the optimal means of suppressing the system [8].

Aliskiren is the first in a new class of oral direct renin inhibitors for the treatment of hypertension. Aliskiren has demonstrated effective BP lowering and was generally well tolerated in short and long-term clinical trials in patients with mild-to-moderate hypertension [10–13]. In a short-term study in patients with type 1 or 2 diabetes and hypertension, aliskiren showed superior reductions in both clinic and ambulatory BP, together with a lower incidence of cough, compared with ramipril [14,15].

This 26-week, randomized, double-blind study compared the efficacy, safety and tolerability of aliskiren and ramipril-based regimens for the treatment of patients with mild-to-moderate hypertension. Ramipril was selected as the comparator treatment as it is one of the most widely prescribed ACE inhibitors and provides effective BP lowering in patients with hypertension [16], demonstrating comparable efficacy to other ACE inhibitors in clinical studies [17,18]. In a meta-analysis of clinical trials, BP reductions with ACE inhibitors were consistent with those seen with other classes of antihypertensive agent (β-blockers, calcium channel blockers, angiotensin receptor blockers and diuretics) [19]. Furthermore, in the Heart Outcomes Prevention Evaluation (HOPE) study, ramipril was associated with marked reductions in cardiovascular mortality and morbidity in patients at high risk of cardiovascular disease [20]. The two ramipril doses (5 and 10 mg) used in the present study were chosen based on the label and common prescribing practice for hypertension in Europe and North America.

## Patients and methods

### Patients

Patients aged 18 years or over with hypertension [mean sitting diastolic BP (msDBP) $\geq 90$ mmHg and $< 110$ mmHg] were eligible for inclusion in the study. Major exclusion criteria included severe hypertension [msDBP $\geq 110$ mmHg or mean sitting systolic BP (msSBP) $\geq 180$ mmHg]; history or evidence of secondary hypertension; known Keith–Wagener grade III or IV hypertensive retinopathy; type 1 or type 2 diabetes mellitus with fasting glycosylated haemoglobin ($HbA_{1c}$) $> 9\%$ at screening; history of severe cerebrovascular or cardiovascular disease; and any condition that may alter the absorption, distribution, metabolism or excretion of study drugs. Pregnant or nursing women were also excluded.

The study was conducted according to the ethical principles of the Declaration of Helsinki. The study protocol and any amendments were reviewed and approved by the Independent Ethics Committee or Institutional Review Board for each study center, and patients provided written informed consent before participating in the study.

### Study design

This randomized, double-blind, multicenter, active and placebo-controlled study was conducted at 92 study centers in nine countries (Belgium, Canada, Hong Kong, Denmark, Iceland, Slovakia, South Africa, Spain and the USA).

#### *Double-blind, active-controlled treatment period*

Following a 2-week washout period for existing antihypertensive medication, patients entered a single-blind, placebo run-in period of up to 4 weeks to establish baseline BP measurements and eligibility for randomization (msDBP $\geq 95$ mmHg and $< 110$ mmHg and a difference of $\leq 10$ mmHg in msDBP from their previous visit) (Fig. 1). Eligible patients were randomized to once-daily treatment with aliskiren 150 mg or ramipril 5 mg. Uptitration to aliskiren 300 mg or ramipril 10 mg, and subsequent addition of hydrochlorothiazide (HCTZ) 12.5 mg and uptitration to HCTZ 25 mg were permitted sequentially for patients not achieving adequate BP control ($< 140/90$ mmHg) at weeks 6, 12, 18 and 21 (Fig. 1).

#### *Double-blind, placebo-controlled withdrawal period*

Patients completing the 26-week active treatment period were re-randomized equally to either their current regimen or placebo for a 4-week, double-blind withdrawal period (Fig. 1).

### Efficacy assessments

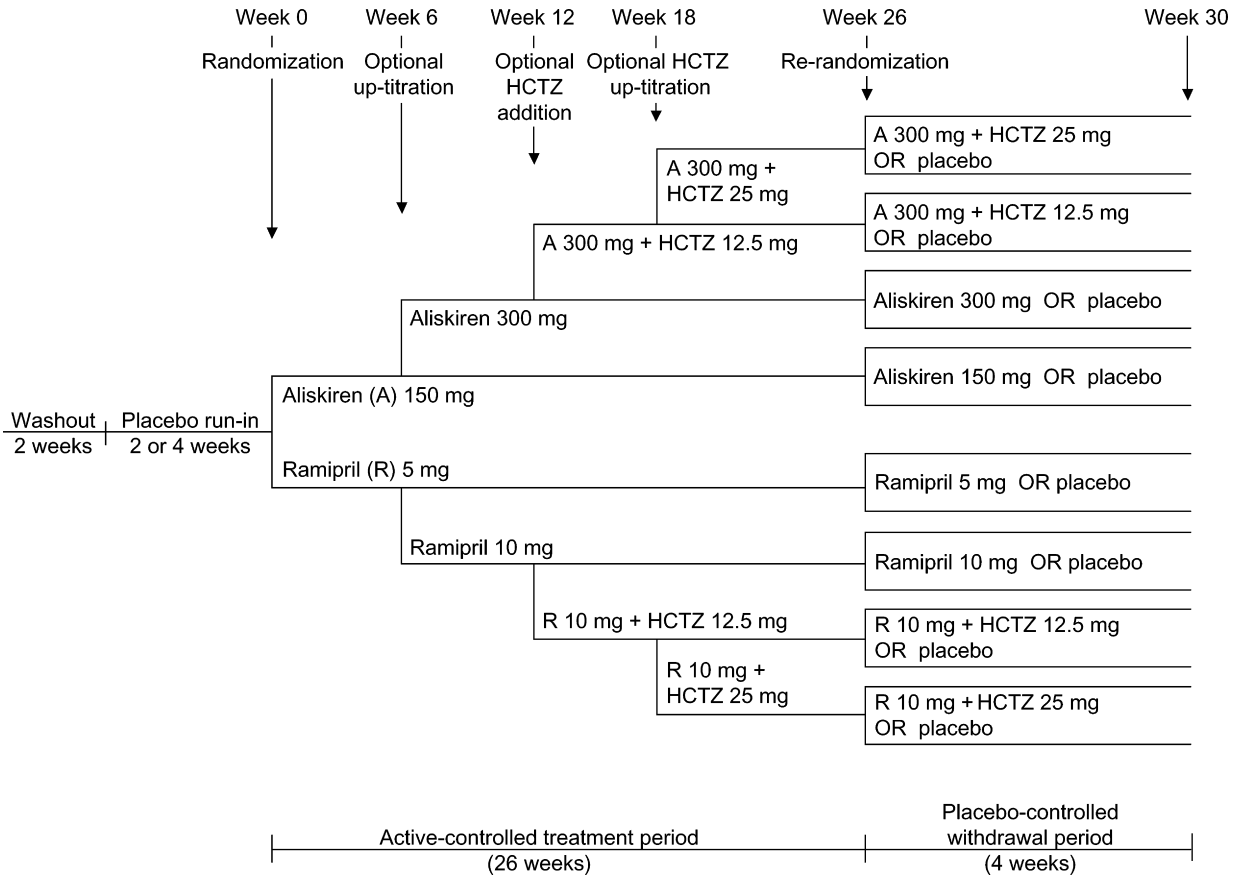
The study compared the BP-lowering efficacy of aliskiren-based and ramipril-based therapy by testing noninferiority and superiority (if noninferiority was achieved) of the aliskiren regimen compared with the ramipril regimen for the changes from baseline in msSBP and msDBP.

The primary efficacy measure was the change from baseline in msDBP at the week 26 endpoint. Secondary efficacy measures included change from baseline in msSBP at week 26 endpoint; change in msSBP and msDBP at week 6 and 12 endpoints (comparing aliskiren and ramipril monotherapy); and the proportions of patients achieving BP control ($< 140/90$ mmHg) at week 6, 12 and 26 endpoints. Additional analysis included systolic BP control ($< 140$ mmHg) at these endpoints. The impact of stopping treatment on BP was evaluated during the withdrawal period.

### Blood pressure measurements

Clinic BP and pulse rate were evaluated at randomization and at weeks 3, 6, 9, 12, 15, 18, 21 and 26 during the

**Fig. 1**




Study design. HCTZ, hydrochlorothiazide.

active-controlled treatment period, then weekly during the withdrawal period. BP was measured using a standard calibrated sphygmomanometer and appropriate arm cuff size in accordance with the 2005 American Heart Association Committee on Blood Pressure Determination. Measurements were taken at trough ($24 \pm 3$ h after dosing) from the arm with the higher sitting SBP measurement at screening. After the patient had been sitting for 5 min, three sitting BP measurements were taken at 1–2 min intervals and the average of these recorded as the mean value for that visit. Following these measurements, a single standing BP measurement was taken. Pulse rate was recorded just prior to the first sitting and the standing BP measurements.

### Safety and tolerability assessments

Adverse events were monitored and recorded at each study visit and assessed by the investigator for their likely relationship to study medication. Other safety assessments, including vital signs measurements, physical examinations, 12-lead ECGs and the monitoring of hematology, blood chemistry and urine test values, were performed at regular intervals during the study.

### Statistical analyses

#### *Double-blind, active-controlled treatment period*

Noninferiority of aliskiren-based therapy versus ramipril-based therapy was assessed using an analysis of covariance (ANCOVA) model with treatment and region as factors and baseline as covariate at weeks 6, 12 and 26 endpoints (noninferiority margin 2 mmHg for msDBP and 4 mmHg for msSBP; one-sided significance level of 0.025). If noninferiority was established, the data were assessed for treatment superiority at a two-sided significance level of 0.05.

The proportion of patients achieving BP control and systolic BP control was compared using a logistic regression model with treatment and region as factors and baseline msDBP as a covariate at week 6, 12 and 26 endpoints. All analyses were performed on the intent-to-treat (ITT) population, defined as all randomized patients who had a baseline and at least one post-baseline efficacy measurement. Last observation carried forward (LOCF) methodology was used for week 6, 12 and 26 endpoint values.

#### *Double-blind, placebo-controlled withdrawal period*

Differences between active treatment and placebo were assessed during the withdrawal period within each antihypertensive regimen. Changes in msSBP and msDBP from withdrawal baseline (week 26) to week 30 endpoint were analyzed (for treatment superiority) using a two-way ANCOVA model, and BP control and systolic BP control rates at week 30 endpoint were assessed by a logistic regression model, as per the primary analysis. The last postwithdrawal baseline msSBP or msDBP measurement during the treatment withdrawal period was carried forward as the week 30 endpoint (LOCF) measurement.

Statistical analyses were performed using SAS software (version 8.2, SAS Institute Inc., Cary, North Carolina, USA). All statistical tests, with the exception of the noninferiority test, were conducted at a two-sided significance level of 0.05.

## Results

### Patient demographics and disposition

Of the 1082 patients enrolled in the study, 239 discontinued during the single-blind, placebo run-in period. The majority of discontinuations ($n = 157$) were for abnormal test results, which included not meeting BP eligibility for randomization (Fig. 2). In total, 842 patients were randomized to aliskiren 150 mg ($n = 420$) or ramipril 5 mg ($n = 422$). Patient demographic characteristics were similar between the two treatment groups (Table 1).

In all, 687 patients (81.6%) completed the 26-week active-controlled treatment period. The main reasons for discontinuation were withdrawal of consent ($n = 56$, 6.7%) and adverse events ($n = 43$, 5.1%; Fig. 2). Few patients in either group discontinued due to unsatisfactory therapeutic effect (overall, $n = 26$; 3.1%). A total of 675 patients entered the withdrawal period: 333 patients were re-randomized to their current aliskiren-based regimen ($n = 170$) or placebo ($n = 163$), and 342 to their current ramipril-based regimen ($n = 165$) or placebo ($n = 177$). Completion rates for the withdrawal period exceeded 90% for all four groups (Fig. 2).

During the active-controlled treatment period, more patients in the ramipril group ($n = 209$, 49.5%) required the addition of HCTZ to their therapy than in the aliskiren group ($n = 193$, 46.1%), although the difference was not statistically significant ($P = 0.334$). Titration of HCTZ therapy to 25 mg occurred in significantly more ramipril-treated patients ($n = 132$, 31.3%) than aliskiren-treated patients ($n = 92$, 22.0%; $P = 0.0024$).

### Efficacy

#### *Active-controlled treatment period*

Aliskiren-based therapy (i.e. aliskiren alone or combined with HCTZ) lowered mean msSBP/msDBP from 151.3/98.8 mmHg at baseline to 133.7/85.8 mmHg at week 26 endpoint (Fig. 3). With ramipril-based therapy, mean BP values decreased from 151.4/98.9 mmHg to 136.4/87.2 mmHg at week 26 endpoint. The mean reductions in msSBP and msDBP at endpoint were significantly greater with aliskiren-based therapy than with ramipril-based therapy ($P = 0.0036$ and $P = 0.025$, respectively) (Table 2).

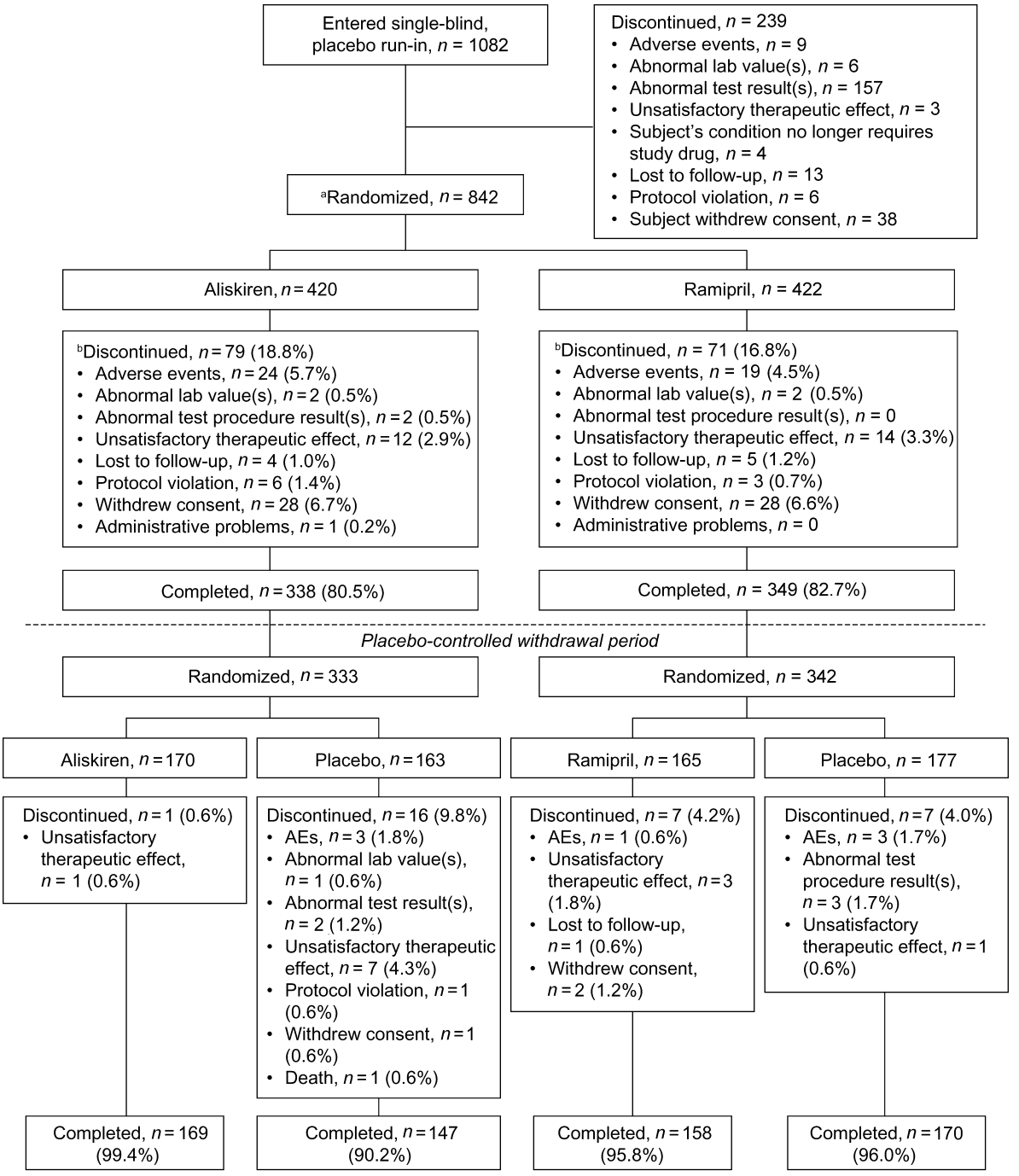
The proportion of patients who had their msSBP controlled to $< 140$ mmHg was significantly higher with aliskiren-based therapy (72.5%) than with ramipril-based therapy (64.1%; $P = 0.0075$) at week 26 endpoint (Fig. 4). The proportion of patients achieving BP $< 140/90$ mmHg was also significantly higher with aliskiren (61.4%) than with ramipril (53.1%; $P = 0.0205$) at this endpoint.

Reductions in mean BP were observed throughout the 26-week active treatment period in both treatment groups, with mean msSBP values decreasing to below 140 mmHg by week 6 in the aliskiren group and week 9 in the ramipril group (Fig. 3). At week 6, before optional uptitration to the higher treatment dose was allowed, and week 12, before the optional addition of HCTZ, the mean reductions in msSBP with aliskiren monotherapy were significantly greater than those achieved with ramipril monotherapy (Table 2). Reductions in msDBP were also larger in the aliskiren group than the ramipril group.

In the subgroup of patients who received only monotherapy during the 26-week treatment period (ITT population, aliskiren $n = 220$; ramipril $n = 209$), mean BP reductions from baseline to week 26 endpoint were similar to those in the overall population (aliskiren 149.8/98.4 to 132.8/85.1 mmHg; ramipril 148.7/98.5 to 135.8/87.0 mmHg). The proportion of patients with msSBP $< 140$ mmHg was higher in the aliskiren than the ramipril monotherapy group at week 26 endpoint (76.8 versus 69.9%; $P = 0.0287$). Mean reductions were greater with aliskiren monotherapy than ramipril monotherapy for msSBP ($16.9 \pm 0.9$ versus $13.2 \pm 1.0$ mmHg; $P = 0.0056$) and msDBP ($13.3 \pm 0.6$ versus $11.6 \pm 0.6$ mmHg; $P = 0.0356$) at week 26. Aliskiren monotherapy also provided effective BP lowering in the subgroup of patients with msSBP $\geq 160$ mmHg at baseline. Mean reductions at week 12 (before optional HCTZ addition) were greater with aliskiren ($n = 88$) than ramipril ($n = 87$) for msSBP ($22.3 \pm 1.5$ versus $18.1 \pm 1.5$ mmHg; $P = 0.0518$) and msDBP ($12.7 \pm 0.9$ versus $10.2 \pm 0.9$ mmHg; $P = 0.0428$).

Post-hoc analyses for the subgroups of patients with metabolic syndrome, obesity or diabetes showed that the mean decreases in msSBP and msDBP with both aliskiren and ramipril-based therapy were generally similar in the subgroups to those observed in the overall study population, although BP reductions with ramipril therapy were slightly larger in the diabetes subgroup than in the overall population (Table 3).

**Fig. 2**




Patient disposition in the active-controlled treatment period and the placebo-controlled withdrawal phase.

***Placebo-controlled withdrawal period***

During the treatment withdrawal period, patients re-randomized to their existing treatment regimen showed minimal mean changes in msSBP and msDBP from withdrawal baseline (i.e., week 26) values over the 4-week period (Fig. 5). For patients switched to placebo, the increases in BP occurred more rapidly after stopping ramipril-based than aliskiren-based therapy, with most of the BP-lowering effect observed with ramipril-based therapy lost at the first week after stopping active

**Table 1 Patient demographics and baseline characteristics (randomized patients)**

| | Aliskiren ($n=420$) | Ramipril ($n=422$) |
|---|---|---|
| Age, years | 53.4 ± 10.8 | 53.1 ± 11.2 |
| ≥65 years, *n* (%) | 64 (15.2) | 63 (14.9) |
| Sex, *n* | | |
| Male/female | 224/196 | 256/166 |
| Race, *n* (%) | | |
| Caucasian | 312 (74.3) | 326 (77.3) |
| Black | 84 (20.0) | 67 (15.9) |
| Asian | 14 (3.3) | 13 (3.1) |
| Other | 10 (2.4) | 16 (3.8) |
| BMI (kg/m$^2$) | 30.3 ± 5.9[a] | 31.4 ± 6.8[b] |
| Obese, *n* (%) | 184 (43.8)[a] | 221 (52.4)[b] |
| Metabolic syndrome, *n* (%) | 171 (40.7) | 183 (43.4)[b] |
| Diabetes, *n* (%) | 42 (10.0) | 49 (11.6) |
| Duration of hypertension (years) | 7.4 ± 6.9[c] | 8.1 ± 7.5[d] |
| msSBP (mmHg) | 151.3 ± 11.7 | 151.5 ± 11.7 |
| msDBP (mmHg) | 98.8 ± 3.4 | 98.9 ± 3.5 |

Data are presented as mean ± SD, unless otherwise stated. Obesity was defined as BMI ≥30 kg/m$^2$. Metabolic syndrome was defined as three or more of the following: waist circumference (>102 cm for men or >88 cm for women); triglycerides ≥150 mg/dl (≥1.69 mmol/l); HDL cholesterol <40 mg/dl (<1.04 mmol/l) for men or <50 mg/dl (<1.29 mmol/l) for women; blood pressure: SBP ≥130 mmHg or DBP ≥85 mmHg; fasting glucose ≥110 mg/dl (≥6.1 mmol/l). BMI, body mass index; msDBP, mean sitting diastolic blood pressure; msSBP, mean sitting systolic blood pressure. [a] $n=418$; [b] $n=421$; [c] $n=410$; [d] $n=411$.

treatment (Fig. 5). As a result, median BP levels reached 140/90 mmHg 1 week after stopping ramipril-based therapy, but did not reach this level until 4 weeks after stopping aliskiren-based treatment.

In the continued active treatment groups, the proportions achieving SBP <140 mmHg (aliskiren, 77.1%; ramipril, 70.6%) and BP <140/90 mmHg (aliskiren, 62.9%; ramipril, 52.8%) were maintained in both treatment groups at week 30 endpoint. At the end of the 4-week withdrawal period, the systolic control rate and overall BP control rate were higher after stopping aliskiren-based treatment (51.5 and 34.4%, respectively) than ramipril-based treatment (40.7 and 26.0%, respectively). The differences between each active treatment and its placebo were statistically significant at endpoint ($P<0.0001$).

### Safety and tolerability

#### *Active-controlled treatment period*

The majority of adverse events reported during the 26-week active treatment period were mild or moderate in intensity and transient, and most events occurred at a similar incidence in the two groups (Table 4). The main exception was cough, which was reported more than twice as frequently by patients receiving ramipril (9.5%) than aliskiren (4.1%). Cough that was judged to be treatment-related by the investigators was also more frequent with ramipril (5.5%) than aliskiren (2.1%). Headache was more common with aliskiren than with ramipril (11.2 versus 8.3%), but the rates of treatment-related headache were low and similar in the two groups (aliskiren, 1.4%; ramipril, 1.7%).

There were few serious adverse events or discontinuations due to adverse events (Table 4). The most frequent reason for discontinuation was cough, which was more common with the ramipril group (2.1%) than aliskiren (1.0%). Only one serious adverse event was considered related to study medication; a case of angioneurotic edema in one patient receiving aliskiren 150 mg, who recovered completely following discontinuation of study medication. One patient died due to mesenteric thrombosis 6 days after discontinuing treatment with ramipril 10 mg plus HCTZ 25 mg; the death was not considered related to study medication.

Clinical laboratory evaluations showed few differences between the treatment groups during active treatment, although the incidence of patients with serum potassium levels >5.5 mmol/l was higher in the aliskiren group (1.9%) than the ramipril group (1.0%) (Table 4). Few patients in either the aliskiren ($n=2$) or ramipril ($n=1$) group exhibited serum potassium of 6.0 mmol/l or higher.

#### *Placebo-controlled withdrawal period*

The incidence of adverse events during the withdrawal period was similar in patients who stopped aliskiren-based therapy (i.e., switched to placebo) and those who continued aliskiren treatment (19.0 and 22.4%, respectively) (Table 4). Rates of adverse events were higher in patients in the ramipril group, whether they stopped (29.4%) or continued (29.7%) active treatment. Adverse events in the primary system organ class infections and infestations were more frequent in the ramipril groups (active, 15.8%; placebo, 11.9%) than in the aliskiren groups (active, 7.1%; placebo, 4.3%). Few patients discontinued due to adverse events during this phase of the study.

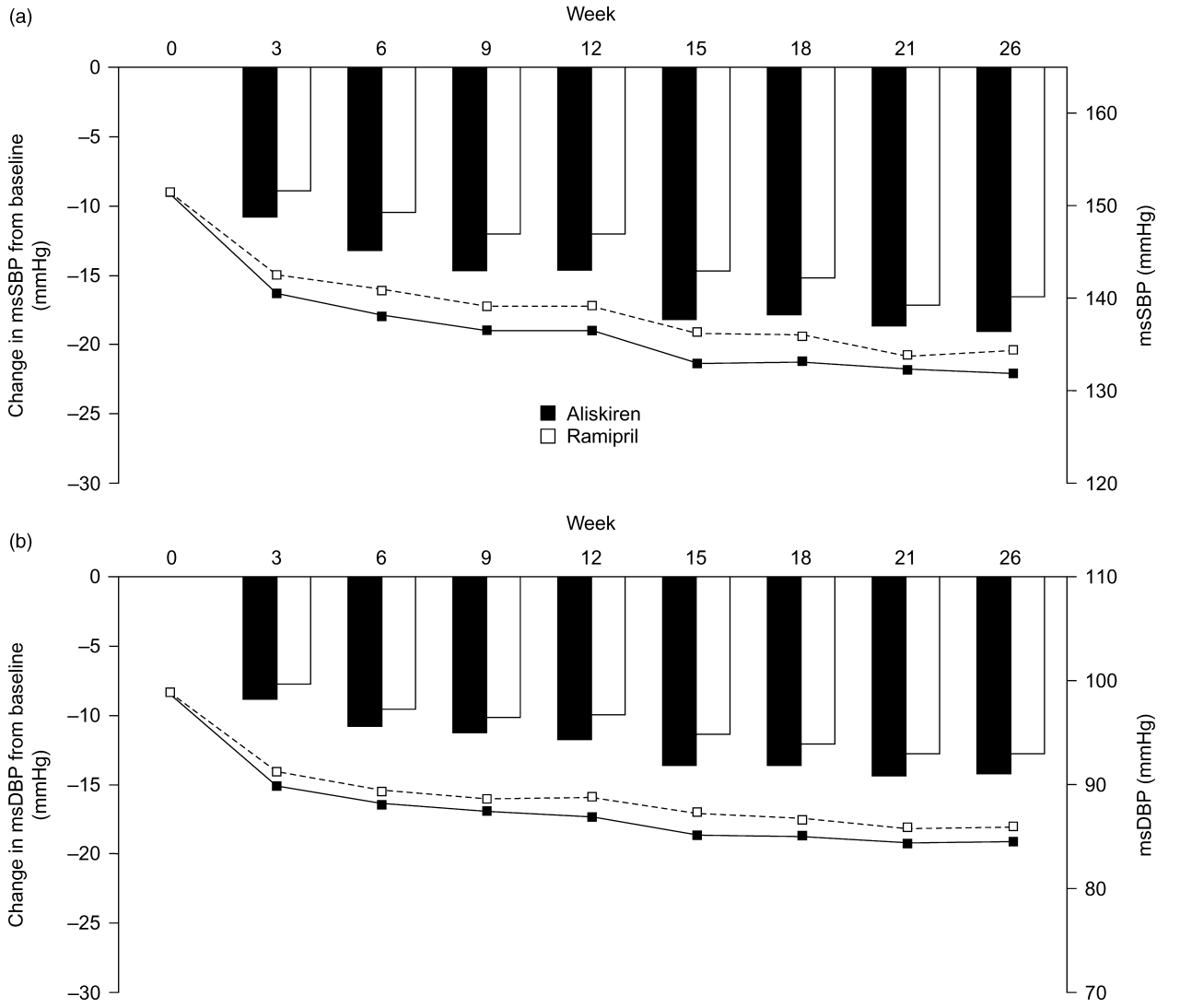
Three patients experienced serious adverse events during the withdrawal period (aliskiren group $n=1$; aliskiren placebo group $n=2$), but none was considered related to study medication. There was one death during the withdrawal period. The patient had been re-randomized from aliskiren 300 mg to placebo, and the cause of death (massive pulmonary embolism or myocardial infarction) was considered to be due to progression of underlying disease and not related to study medication.

Changes in biochemistry and hematology parameters during the withdrawal period were small, with no clinically meaningful differences observed between the treatment groups. Few patients experienced abnormal laboratory values (Table 4).

## Discussion

This is the first long-term study to compare the antihypertensive efficacy, safety and tolerability of the direct renin inhibitor aliskiren with an active comparator, the ACE inhibitor ramipril. In this study, aliskiren-based

**Fig. 3**




Mean values and mean changes from baseline in (a) mean sitting systolic blood pressure (msSBP) and (b) mean sitting diastolic blood pressure (msDBP) during active-controlled treatment period. Mean values are shown by solid (aliskiren) or dashed (ramipril) lines; mean changes from baseline are shown by filled (aliskiren) or open (ramipril) bars. At each time point, only patients with available data at that time point are included.

**Table 2 Least-squares mean change (SEM) from baseline in mean sitting systolic and diastolic blood pressure at week 6, 12 and 26 endpoints**

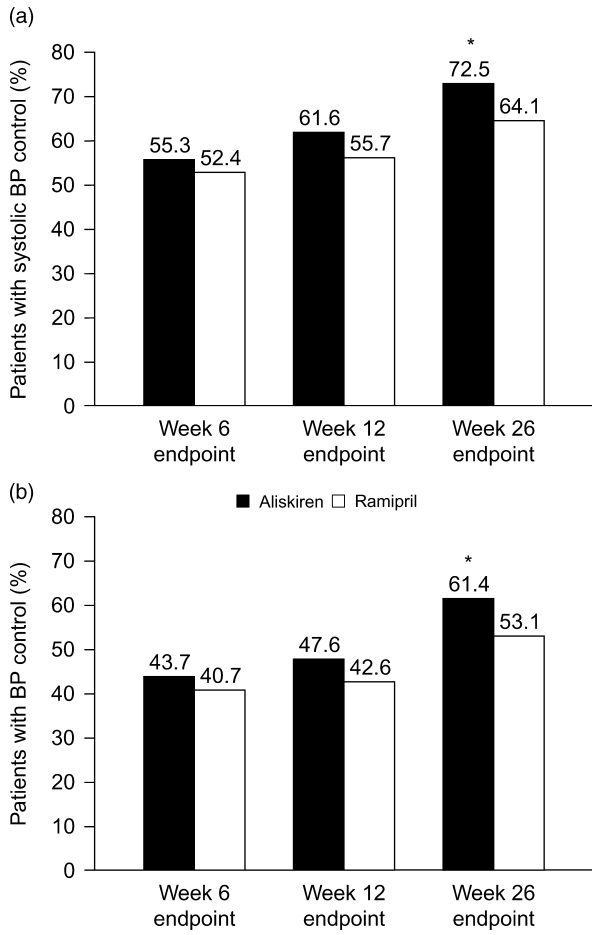
| | Aliskiren ($n=414$) | Ramipril ($n=418$) | $P$-value* |
|---|---|---|---|
| msSBP | | | |
| Week 6 endpoint | −12.9 (0.6) | −10.5 (0.6) | 0.0041 |
| Week 12 endpoint | −14.0 (0.6) | −11.3 (0.6) | 0.0027 |
| Week 26 endpoint | −17.9 (0.7) | −15.2 (0.6) | 0.0036 |
| msDBP | | | |
| Week 6 endpoint | −10.5 (0.4) | −9.5 (0.4) | 0.0689 |
| Week 12 endpoint | −11.3 (0.4) | −9.7 (0.4) | 0.0056 |
| Week 26 endpoint | −13.2 (0.4) | −12.0 (0.4) | 0.0250 |

*Two-sided statistical significance test for treatment superiority, analyzed by ANCOVA. Aliskiren was statistically noninferior ($P<0.0001$) to ramipril for all comparisons (one-sided statistical significance at 0.025 level for treatment noninferiority, analyzed by ANCOVA). msDBP, mean sitting diastolic blood pressure; msSBP, mean sitting systolic blood pressure.

treatment (i.e., aliskiren alone or combined with HCTZ) produced sustained lowering of BP over the 26-week active-controlled treatment period, with greater reductions observed at almost all assessments than with ramipril-based therapy. Rates of systolic BP control (msSBP $<140$ mmHg) were significantly higher with aliskiren-based therapy compared with ramipril-based therapy at week 26. Aliskiren-based treatment was generally well tolerated throughout the study period.

After 6 months, mean BP was reduced to 133.7/85.8 mmHg with the aliskiren-based regimen, and 136.4/87.2 mmHg with the ramipril-based regimen. The reductions in systolic and diastolic BP with the aliskiren-based regimen were significantly greater than

**Fig. 4**




(a) Systolic blood pressure (BP) control rates and (b) BP control rates with aliskiren-based and ramipril-based treatment at week 6, 12 and 26 endpoints. Systolic BP control was defined as mean sitting systolic BP (msSBP) <140 mmHg; BP control was defined as msSBP/mean sitting diastolic BP (msDBP) <140/90 mmHg. *$P < 0.05$ versus ramipril (two-sided test for significance, analyzed by logistic regression model).

those observed with ramipril-based treatment. Aliskiren monotherapy also showed improved BP-lowering efficacy over ramipril monotherapy before the optional addition of HCTZ at week 12 and in the subgroup of patients who did not require HCTZ addition during the 26-week treatment period.

The proportions of patients in the aliskiren group achieving systolic BP control and overall BP control were significantly greater than in the ramipril group at week 26. In addition, fewer patients required the addition of HCTZ to their initial therapy or titration to the 25 mg HCTZ dose in the aliskiren group compared with the ramipril group, a further indication of the greater antihypertensive efficacy of aliskiren over ramipril. The proportion of patients requiring the addition of HCTZ to aliskiren therapy (46%) in order to achieve BP control was similar to that observed with aliskiren in a previous long-term, open-label study (45%) [13]. Combination therapy is needed to achieve BP control in the majority of patients with hypertension [3,21] and thiazide diuretics, such as HCTZ, are widely used in combination regimens [22]. In large-scale trials of patients with mild-to-moderate hypertension, approximately two-thirds of patients required combination treatment to achieve BP control [23–25]. The findings of the present study show that aliskiren in combination with HCTZ is a highly effective BP-lowering treatment option.

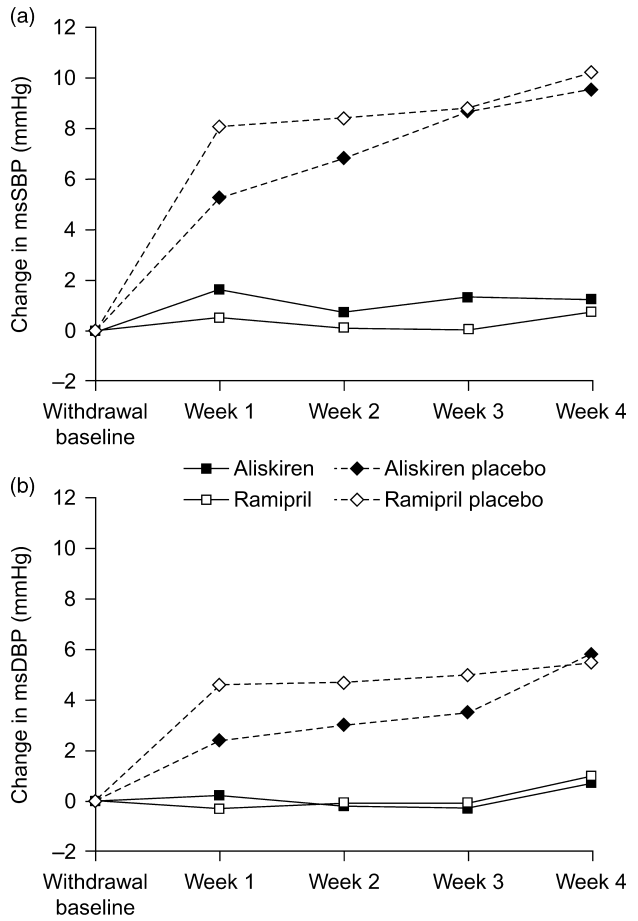
Post-hoc analyses also showed that the antihypertensive efficacy of aliskiren-based therapy was similar or slightly greater than ramipril-based therapy in the subgroups of patients with obesity or metabolic syndrome. The BP reductions observed with both treatments in patients with obesity and metabolic syndrome were similar to those observed for the overall study population. For the subgroup of patients with diabetes, BP reductions with ramipril treatment were actually slightly greater than in the overall population. Thus there is no evidence to suggest that the small differences in the baseline patient characteristics between the two treatment groups

**Table 3 Least-squares (LS) mean change (SEM) from baseline in mean sitting systolic and diastolic blood pressure and control rates at week 26 endpoint for the subgroups of patients with obesity, metabolic syndrome or diabetes**

| | Obesity (BMI $\geq$ 30 kg/m$^2$) | | Metabolic syndrome | | Diabetes | |
|---|---|---|---|---|---|---|
| | Aliskiren ($n$ = 184) | Ramipril ($n$ = 219) | Aliskiren ($n$ = 168) | Ramipril ($n$ = 182) | Aliskiren ($n$ = 42) | Ramipril ($n$ = 49) |
| msSBP (mmHg) | | | | | | |
| Baseline | 151.6 ± 11.8 | 151.7 ± 11.8 | 151.9 ± 12.1 | 151.3 ± 11.9 | 155.2 ± 10.3 | 151.9 ± 11.7 |
| Endpoint | 135.3 ± 15.1 | 137.0 ± 13.9 | 134.5 ± 14.9 | 136.8 ± 14.2 | 136.8 ± 15.0 | 135.7 ± 9.3 |
| LS mean change (SEM) | 16.6 (1.0) | 14.9 (0.9) | 17.3 (1.0) | 14.8 (0.9) | 16.9 (2.0) | 17.2 (1.8) |
| msDBP (mmHg) | | | | | | |
| Baseline | 99.0 ± 3.3 | 99.2 ± 3.7 | 99.0 ± 3.4 | 99.0 ± 3.5 | 98.7 ± 3.2 | 98.6 ± 3.2 |
| Endpoint | 86.9 ± 9.5 | 88.5 ± 9.2 | 86.5 ± 9.1 | 87.1 ± 8.1 | 86.3 ± 9.3 | 86.2 ± 7.0 |
| LS mean change (SEM) | 12.2 (0.6) | 10.9 (0.6) | 12.6 (0.6) | 11.9 (0.6) | 12.4 (1.3) | 12.6 (1.2) |
| SBP < 140 mmHg (%) | 67.4 | 59.8 | 69.0 | 62.6 | 61.9 | 65.3 |
| BP < 140/90 mmHg (%) | 57.1 | 48.4 | 57.7 | 50.5 | 52.4 | 53.1 |

Data are presented as mean ± SD, unless otherwise stated. BMI, body mass index; msDBP, mean sitting diastolic blood pressure; msSBP, mean sitting systolic blood pressure.

**Fig. 5**




Change in (a) mean sitting systolic blood pressure (msSBP) and (b) mean sitting diastolic blood pressure (msDBP) for patients continuing active treatment (solid lines) and patients switched to placebo (dashed lines) during the 4-week withdrawal period. Data are mean change from withdrawal baseline (i.e. week 26) value. Mean blood pressure at withdrawal baseline: aliskiren 130.7/83.8 mmHg; aliskiren placebo 132.3/85.1 mmHg; ramipril 134.0/86.3 mmHg; ramipril placebo 133.6/85.3 mmHg.

will have affected the overall results of the study. The differences in BP lowering at trough observed between aliskiren and ramipril could have been affected by the shorter duration of action of ramipril compared to aliskiren. From a clinical perspective, however, antihypertensive treatments need to provide effective BP control throughout the 24-h dosing period. Thus the superiority of aliskiren over ramipril in reducing trough BP is a clinically important finding, irrespective of the underlying reason for the difference.

The reduction in BP seen with the aliskiren regimen during the 26-week study was maintained with continued aliskiren treatment during the withdrawal period. In patients who switched from aliskiren-based therapy to placebo for the withdrawal period, there was only a gradual loss of the reductions in BP achieved during active aliskiren treatment. In contrast, patients switched from ramipril-based therapy to placebo showed a more rapid loss of BP-lowering effect, with BP returning to near baseline levels during the first week after withdrawal. Thus, median BP values reached 140/90 mmHg 1 week after stopping ramipril therapy, but did not reach this level until 4 weeks after stopping aliskiren. The increases in BP observed after stopping treatment demonstrate the sensitivity of the study, and indicate that the study treatments continued to be effective after 6 months of therapy. The sustained BP-lowering effects of antihypertensive medication after stopping therapy may be of value in minimizing the effects of occasional poor compliance with prescribed treatment.

Aliskiren treatment was well tolerated over the 6-month active-controlled treatment period. The majority of adverse events were mild or moderate in severity, and the type and incidence of adverse events was generally similar in the two treatment groups. The major exception was cough, which was reported more than twice as frequently with ramipril therapy than with aliskiren. Similar findings were observed in a previous aliskiren study involving patients with diabetes and hypertension [14], and are consistent with the known side-effect profile of ACE inhibitors [26]. Estimates suggest that around 10% of patients develop cough with ACE inhibitor therapy, and that it may lead to treatment withdrawal in approximately half of these patients [27,28]. The occurrence of ACE inhibitor-induced cough may impact on patient quality of life [28], although some studies suggest that it has little effect on patient well being [29,30]. Headache was more frequent with aliskiren than ramipril therapy, although the proportion of events considered to be related to study medication was low and similar in the two groups.

Aliskiren continued to show good tolerability throughout the withdrawal period, with a similar incidence of adverse events in patients who continued on aliskiren compared with those who switched to placebo. The incidence of adverse events was lower in both of these groups than in patients who continued or stopped ramipril therapy. Analysis of biochemical laboratory parameters during the active-controlled treatment period or the withdrawal period showed that approximately 5% of patients in each group had potassium levels under 3.5 mmol/l, which is not unexpected with HCTZ-containing treatment regimens [31,32]. Few patients in either group exhibited potassium levels over 5.5 mmol/ ($< 2\%$) or $\geq 6.0$ mmol/l ($\leq 0.5\%$).

In conclusion, aliskiren-based treatment (alone or in combination with HCTZ) provided long-term reductions in BP that were larger than those observed with a regimen based on the ACE inhibitor ramipril in patients with hypertension. These BP reductions persisted for longer after stopping aliskiren-based therapy than ramipril-based

**Table 4 Adverse events during the active-controlled treatment period and the withdrawal period**

| Active-controlled treatment period | Aliskiren ($n=419$) | Ramipril ($n=422$) |
|---|---|---|
| Any AE | 257 (61.3) | 255 (60.4) |
| Any SAE | 8 (1.9) | 6 (1.4) |
| Discontinuation due to AEs | 24 (5.7) | 20 (4.7) |
| Frequently reported AEs ($\geq$2% in any group) | | |
| Headache | 47 (11.2) | 35 (8.3) |
| Nasopharyngitis | 25 (6.0) | 26 (6.2) |
| Dizziness | 23 (5.5) | 20 (4.7) |
| Fatigue | 18 (4.3) | 15 (3.6) |
| Cough | 17 (4.1) | 40 (9.5) |
| Diarrhea | 16 (3.8) | 7 (1.7) |
| Peripheral edema | 16 (3.8) | 13 (3.1) |
| Back pain | 15 (3.6) | 13 (3.1) |
| Pain in extremity | 15 (3.6) | 8 (1.9) |
| Bronchitis | 13 (3.1) | 4 (0.9) |
| URTI | 12 (2.9) | 17 (4.0) |
| Nausea | 11 (2.6) | 8 (1.9) |
| Dyspepsia | 10 (2.4) | 4 (0.9) |
| Sinusitis | 8 (1.9) | 10 (2.4) |
| Influenza | 6 (1.4) | 11 (2.6) |
| Laboratory abnormalities | | |
| Potassium $<3.5$ mmol/l | 22 (5.3) | 19 (4.6) |
| Potassium $>5.5$ mmol/l | 8 (1.9) | 4 (1.0) |
| Potassium $\geq 6.0$ mmol/l | 2 (0.5) | 1 (0.2) |
| BUN $>14.28$ mmol/l | 1 (0.2) | 1 (0.2) |
| Creatinine $>176.8$ μmol/l | 0 | 3 (0.7) |

| Withdrawal period | Aliskiren ($n=170$) | Placebo ($n=163$) | Ramipril ($n=165$) | Placebo ($n=177$) |
|---|---|---|---|---|
| Any AE | 38 (22.4) | 31 (19.0) | 49 (29.7) | 52 (29.4) |
| Any SAE | 1 (0.6) | 2 (1.2) | 0 | 0 |
| Discontinuation due to AEs | 0 | 4 (2.5) | 1 (0.6) | 3 (1.7) |
| Frequently reported AEs ($\geq$ 2% in any group) | | | | |
| Headache | 3 (1.8) | 7 (4.3) | 3 (1.8) | 14 (7.9) |
| URTI | 3 (1.8) | 2 (1.2) | 7 (4.2) | 2 (1.1) |
| Nasopharyngitis | 2 (1.2) | 1 (0.6) | 8 (4.8) | 9 (5.1) |
| Laboratory abnormalities | | | | |
| Potassium $<3.5$ mmol/l | 9 (5.6) | 2 (1.3) | 12 (7.6) | 6 (3.5) |
| Potassium $>5.5$ mmol/l | 1 (0.6) | 0 | 3 (1.9) | 0 |
| Potassium $\geq 6.0$ mmol/l | 0 | 0 | 1 (0.6) | 0 |
| BUN $>14.28$ mmol/l | 0 | 0 | 0 | 1 (0.6) |
| Creatinine $>176.8$ μmol/l | 0 | 0 | 0 | 0 |

The number of patients with both baseline and postbaseline values for each laboratory parameter was as follows: active-controlled treatment: aliskiren, all parameters, $n=412$; ramipril, potassium, $n=417$; BUN and creatinine, $n=418$. Withdrawal period (all parameters): aliskiren, $n=162$; aliskiren placebo, $n=156$; ramipril, $n=157$; ramipril placebo, $n=170$. AE, adverse event; SAE, serious adverse event; URTI, upper respiratory tract infection; BUN, blood urea nitrogen.

therapy. Aliskiren therapy was well tolerated during long-term treatment, suggesting the potential for good patient compliance with aliskiren treatment. These results suggest that aliskiren will be an important new addition to the existing treatment options for hypertension.

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## References

1 Kannel WB. Blood pressure as a cardiovascular risk factor: prevention and treatment. *JAMA* 1996; **275**:1571–1576.
2 Collins R, MacMahon S. Blood pressure, antihypertensive drug treatment and the risks of stroke and of coronary heart disease. *Br Med Bull* 1994; **50**:272–298.
3 Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, *et al.* Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003; **42**:1206–1252.
4 Lloyd-Jones DM, Evans JC, Levy D. Hypertension in adults across the age spectrum: current outcomes and control in the community. *JAMA* 2005; **294**:466–472.
5 Wolf-Maier K, Cooper RS, Kramer H, Banegas JR, Giampaoli S, Joffres MR, *et al.* Hypertension treatment and control in five European countries, Canada, and the United States. *Hypertension* 2004; **43**:10–17.
6 European Society of Hypertension-European Society of Cardiology. 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003; **21**:1011–1053.
7 Maibaum J, Feldman D. Renin inhibitors as novel treatments for cardiovascular disease. *Expert Opin Ther Pat* 2003; **13**:589–603.
8 Fisher ND, Hollenberg NK. Renin inhibition: what are the therapeutic opportunities? *J Am Soc Nephrol* 2005; **16**:592–599.

9 Wolny A, Clozel JP, Rein J, Mory P, Vogt P, Turino M, *et al.* Functional and biochemical analysis of angiotensin II-forming pathways in the human heart. *Circ Res* 1997; **80**:219–227.
10 Weir MR, Bush C, Anderson DR, Zhang J, Keefe DL, Satlin A. Antihypertensive efficacy, safety and tolerability of the oral direct renin inhibitor aliskiren in patients with hypertension: a pooled analysis. *J Am Soc Hypertens* 2007; **1**:264–277.
11 Gradman AH, Schmieder RE, Lins RL, Nussberger J, Chiang Y, Bedigian MP. Aliskiren, a novel orally effective renin inhibitor, provides dose-dependent antihypertensive efficacy and placebo-like tolerability in hypertensive patients. *Circulation* 2005; **111**:1012–1018.
12 Oh BH, Mitchell J, Herron J, Chung J, Khan M, Keefe DL. Aliskiren, an oral renin inhibitor, provides dose-dependent efficacy and sustained 24-h blood pressure control in patients with hypertension. *J Am Coll Cardiol* 2007; **49**:1157–1163.
13 Sica D, Gradman AH, Lederballe O, Meyers M, Cai J, Keefe DL. Aliskiren, a novel renin inhibitor, is well tolerated and has sustained BP-lowering effects alone or in combination with HCTZ during long-term (52 weeks) treatment of hypertension [abstract]. *Eur Heart J* 2006; **27 (Suppl)**:121.
14 Uresin Y, Taylor A, Kilo C, Tschope D, Santonastaso M, Ibram G, *et al.* Aliskiren, a novel renin inhibitor, has greater BP lowering than ramipril and additional BP lowering when combined with ramipril in patients with diabetes and hypertension [abstract]. *J Hypertens* 2006; **24 (Suppl 4)**:S82.
15 Taylor A, Tschope D, Kilo C, Ibram G, Fang H, Satlin A. Adding aliskiren to ramipril improves 24-h blood pressure control compared to ramipril alone in patients with diabetes and hypertension [abstract]. *J Hypertens* 2006; **24 (Suppl 4)**:S81–S82.
16 Frampton JE, Peters DH. Ramipril. An updated review of its therapeutic use in essential hypertension and heart failure. *Drugs* 1995; **49**:440–466.
17 Yasky J, Verho M, Erasmus TP, Luus HG, Angela M, Grandin L, *et al.* Efficacy of ramipril versus enalapril in patients with mild to moderate essential hypertension. *Br J Clin Pract* 1996; **50**:302–310.
18 Ruddy MC, Mroczek WJ. Comparison of ramipril and enalapril in patients with essential hypertension. *Pharmacotherapy* 1993; **13**:224–228.
19 Law MR, Wald NJ, Morris JK, Jordan RE. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. *BMJ* 2003; **326**:1427.
20 Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000; **342**:145–153.
21 Williams B, Poulter NR, Brown MJ, Davis M, McInnes GT, Potter JF, *et al.* British Hypertension Society guidelines for hypertension management 2004 (BHS-IV): summary. *BMJ* 2004; **328**:634–640.
22 Neutel JM, Black HR, Weber MA. Combination therapy with diuretics: an evolution of understanding. *Am J Med* 1996; **101 (3A)**:61S–70S.
23 Cushman WC, Ford CE, Cutler JA, Margolis KL, Davis BR, Grimm RH, *et al.* Success and predictors of blood pressure control in diverse North American settings: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *J Clin Hypertens (Greenwich)* 2002; **4**:393–404.
24 Dahlof B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, *et al.* Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; **359**:995–1003.
25 Black HR, Elliott WJ, Neaton JD, Grandits G, Grambsch P, Grimm RH Jr, *et al.* Baseline characteristics and early blood pressure control in the CONVINCE Trial. *Hypertension* 2001; **37**:12–18.
26 Israili ZH, Hall WD. Cough and angioneurotic edema associated with angiotensin-converting enzyme inhibitor therapy. A review of the literature and pathophysiology. *Ann Intern Med* 1992; **117**:234–242.
27 Yeo WW, Ramsay LE. Persistent dry cough with enalapril: incidence depends on method used. *J Hum Hypertens* 1990; **4**:517–520.
28 Fletcher AE, Palmer AJ, Bulpitt CJ. Cough with angiotensin converting enzyme inhibitors: how much of a problem? *J Hypertens Suppl* 1994; **12**:S43–S47.
29 Omvik P, Thaulow E, Herland OB, Eide I, Midha R, Turner RR. Double-blind, parallel, comparative study on quality of life during treatment with amlodipine or enalapril in mild or moderate hypertensive patients: a multicentre study. *J Hypertens* 1993; **11**:103–113.
30 Breeze E, Rake EC, Donoghue MD, Fletcher AE. Comparison of quality of life and cough on eprosartan and enalapril in people with moderate hypertension. *J Hum Hypertens* 2001; **15**:857–862.
31 Licht JH, Haley RJ, Pugh B, Lewis SB. Diuretic regimens in essential hypertension. A comparison of hypokalemic effects, BP control, and cost. *Arch Intern Med* 1983; **143**:1694–1699.
32 Greenberg A. Diuretic complications. *Am J Med Sci* 2000; **319**:10–24.