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ORIGINAL ARTICLE

Maintenance of blood-pressure-lowering effect following a missed dose of aliskiren, irbesartan or ramipril: results of a randomized, double-blind study

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Most patients inadvertently miss an occasional dose of antihypertensive therapy, and hence drugs that provide sustained blood-pressure (BP) reduction beyond the 24-h dosing interval are desirable. The primary objective of this study was to compare the 24-h mean ambulatory BP reductions from baseline after a simulated missed dose of the direct renin inhibitor aliskiren, irbesartan or ramipril. In this double-blind study, 654 hypertensive patients (24-h mean ambulatory diastolic BP (MADBP) $\geqslant$85 mm Hg) were randomized 1:1:1 to once-daily aliskiren 150 mg, irbesartan 150 mg or ramipril 5 mg. Doses were doubled after 2 weeks. At day 42, patients were again randomized equally within each group to receive 1 day of placebo ('missed dose') on either day 42 or day 49. Patients with a successful 24-h ambulatory BP measurement at baseline and on day 42/49 were included in the analyses. The 24-h mean ambulatory systolic BP (MASBP)/MADBP reductions from baseline after a missed dose of aliskiren 300 mg (9.3/7.0 mm Hg) were similar to irbesartan 300 mg (9.5/7.3 mm Hg) and significantly larger than ramipril 10 mg (7.1/5.0 mm Hg, $P\leqslant0.008$). Loss of BP-lowering effect with aliskiren in the 24 h after a missed dose (1.0/0.7 mm Hg for 24–48-h vs 0–24-h MASBP/MADBP) was significantly lower than with irbesartan (3.6/2.2 mm Hg, $P<0.01$) or ramipril (4.0/2.6, $P<0.0001$). This equates to maintenance of 91/91% of the MASBP/MADBP-lowering effect with aliskiren, greater than irbesartan (73/77%) or ramipril (64/65%). The incidence of adverse events was similar across treatments (32.9–36.0%), although ramipril treatment was associated with an increased incidence of cough (ramipril, 6.1%; aliskiren, 0.5%; irbesartan, 1.8%). Aliskiren 300 mg provided a sustained BP-lowering effect beyond the 24-h dosing interval, with a significantly smaller loss of BP-lowering effect in the 24–48 h period after dose than irbesartan 300 mg or ramipril 10 mg.
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Introduction

The failure of patients to take their blood-pressure (BP)-lowering medications according to prescription (non-adherence) and the discontinuation of treatment altogether (non-persistence) by patients are major contributors to the failure to achieve adequate BP control in clinical practice.[1] In a cross-sectional study of 1503 patients taking one or more antihypertensive medications, the most common reason cited for failing to take treatment 'precisely as prescribed' was forgetfulness (46%).[2] As non-adherence is predominantly unintentional, the need for long-acting BP-lowering agents is important to ensure that rates of BP control are maintained in the event of an occasional missed dose.

The risks associated with occasional non-adherence to antihypertensive therapy have not been studied in similar detail. However, it is well established that sustained BP control throughout the 24-h dosing interval is required for effective reductions in cardiovascular risk,[3] and this would be lost during periods of non-adherence. Importantly, it is now clear that non-adherence to antihypertensive treatment is prevalent even in patients who show good long-term persistence. A study of 4783 patients with hypertension, in which electronic monitors were used to record dosing times and dates, showed that approximately 10%

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of patients omitted to take their prescribed dose of antihypertensive treatment on any given day. Moreover, approximately 18% of patients missed on average at least a single dose each week, and 50% missed at least one dose each month.[4] These findings indicate a clear need for antihypertensive treatments that provide sustained BP reductions beyond the 24-h dosing interval.

Aliskiren, the first in a new class of direct renin inhibitors approved for the treatment of hypertension, provides highly effective BP reduction when administered as monotherapy or in combination with other antihypertensive drug classes.[5] Aliskiren exhibits a long terminal elimination half-life of approximately 40 h,[6,7] and has shown effective 24-h BP control in ambulatory BP-monitoring substudies.[8] Moreover, clinical studies in patients with hypertension have shown that the effect of aliskiren to lower BP and reduce plasma renin activity (PRA) persists for up to 2 weeks after stopping treatment.[8,9] We report the results of an ambulatory BP-monitoring study designed to assess the antihypertensive efficacy of aliskiren following simulated non-adherence (missed doses) of treatment compared with that of the angiotensin receptor blocker (ARB), irbesartan, and the angiotensin-converting enzyme (ACE) inhibitor, ramipril.

Materials and methods

Patients

Patients with hypertension who were 18 years of age or older with an office mean sitting diastolic BP (msDBP) of $\geqslant 90$ and <110 mm Hg were enrolled in the study. Patients were randomized to active treatment if they exhibited a 24-h mean ambulatory diastolic BP (MADBP) $\geqslant 85$ mm Hg. Female patients had to be either post-menopausal for $\geqslant 1$ year, surgically sterile or using effective contraception.

Key exclusion criteria were severe hypertension (office systolic BP (SBP)/DBP $\geqslant 180/110$ mm Hg), secondary hypertension, severe cardiac or cerebrovascular disease, history of type I or type II diabetes with glycosylated haemoglobin (HbA_{1C}) $>8\%$ at screening or an upper arm circumference >42 cm. Patients were also excluded if they had any condition that might significantly alter the pharmacokinetics or pharmacodynamics of the study drugs.

All patients provided written informed consent. The study protocol was approved by the appropriate local ethical committee or institutional review boards and the study was conducted in accordance with ICH Harmonized Tripartite Guidelines for Good Clinical Practice and the Declaration of Helsinki Principles.

Study design

This was a 9-week randomized, parallel-group study in patients with hypertension that was conducted at 97 centres in Brazil, Canada, Germany, Hungary, Italy, the Netherlands, Norway, Russia, Slovakia and Spain. The first patient was enrolled on 31 May 2006 and the last patient was enrolled on 3 May 2007. A full list of principal investigators is provided in the Appendix.

Following a 1-week washout period during which patients were tapered off their current antihypertensive medication, patients entered a 2-week single-blind, placebo run-in phase to establish a baseline BP and assess eligibility for randomization into the study. To remain eligible, DBP had to remain $\geqslant 95$ and <110 mm Hg following the run-in, with an absolute difference of $\leqslant 10$ mm Hg between msDBP measurements. Patients were provided with automated BP devices to establish baseline self-measured BP at home (three times in the morning and three times in the evening) during the single-blind period.

Ambulatory BP-monitoring period (days 1–49)

Eligible patients were randomized in a double-blind manner to receive once-daily treatment with aliskiren 150 mg, irbesartan 150 mg or ramipril 5 mg. On day 14, active treatments were up-titrated to double the initial dose (aliskiren 300 mg, irbesartan 300 mg and ramipril 10 mg, respectively) for 4 weeks. On day 42, patients were randomized equally within each treatment group to receive 1 day of placebo (simulating a missed dose) on either day 42 or day 49; active treatment was continued on all other days (days 42–49).

Randomization was achieved using the interactive voice recording system provider, which automates the random assignment of patient numbers to randomization numbers linked to the different treatment arms, and in turn to medication numbers. A separate medication randomization list was produced by Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to medication packs containing each of the study drugs.

Simulated non-adherence period (self-measured BP; days 50–63)

Patients continued to take their medication during the simulated non-adherence period of the study (days 50–63); treatment was interrupted with a single-blind placebo on days 54 and 55 and days 61 and 62. Patients were provided with automated BP devices to self-measure BP during this period.

Aliskiren was supplied as film-coated 150 mg tablets, and irbesartan and ramipril were supplied as hard gelatin capsules (irbesartan 150 mg and ramipril 5 or 10 mg). For the run-in phase, placebo was provided as a matching film-coated tablet or hard gelatin capsule. To maintain blinding, all patients were required to take two tablets and three capsules of study medication once daily throughout the study. Patients were instructed to take each dose

with water at approximately 0800 hours, except on the morning of an office/clinic visit (when the dose was taken after completing all required evaluations).

Study objectives
The primary objective of the study was to compare the change from baseline in 24-h MADBP following a missed dose of treatment for aliskiren vs irbesartan and aliskiren vs ramipril. Secondary study objectives included the same pair-wise comparisons for the change from baseline in 24-h mean ambulatory systolic BP (MASBP), and in daytime or night-time MADBP or MASBP following a missed dose of treatment. The difference between 24-h ambulatory BP monitoring (ABPM) profiles after a missed dose compared with an active dose was also assessed for each treatment.

Based on a standard deviation (s.d.) of 7.5 mm Hg in the change in 24-h MADBP from baseline, a target sample size of 489 completers (654 randomized patients, assuming a dropout rate of 25%) provided $\geqslant$85% power to detect a treatment difference in MADBP of 2.5 mm Hg between patients receiving aliskiren 300 mg and those receiving irbesartan 300 mg or ramipril 10 mg.

Other study objectives included changes in self-measured BP during simulated non-adherence (two successive missed doses), measurement of the effect of active treatments on PRA and plasma renin concentration (PRC), and the safety and tolerability of study treatments.

BP measurements
Clinic sitting BP was measured at each clinic visit at trough (24 ± 3 h after dose) in the arm in which the highest msDBP was found at the first study visit using a mercury sphygmomanometer. Three sitting BP measurements were taken at 1–2-min intervals and the mean value was taken as the average BP for that visit.

Ambulatory BP monitoring
Mean ambulatory BP (MABP) was assessed over 24 h at baseline (day -1) for eligible patients, and on days 42 and 49 after patients had received double-blind active treatment or placebo. If the measurement of MABP was unsuccessful on day -1, a repeat measurement was permitted within 24–72 h provided that the patient continued to receive single-blind medication. Repeat ABPM was not permitted on day 42 or 49. ABPM set-up and calibration was performed between 0700 and 1000 hours using a SpaceLabs 90207 oscillometric device (SpaceLabs Medical Inc., Redmond, WA, USA) applied to the patient's non-dominant arm. Validity criteria for ABPM measurements included minimum valid SBP 60 mm Hg, maximum valid SBP 261 mm Hg, minimum valid SBP–DBP difference 20 mm Hg, maximum valid SBP–DBP difference 140 mm Hg.

Quality control criteria for ABPM recordings were evaluated automatically by Medicom ABPM software. Minimum quality control criteria were: (1) beginning of ABPM recording no earlier than 0700 hours and no later than 1000 hours, (2) a minimum duration of 24 h of BP data following the beginning of ABPM recording, (3) a minimum of 70% of the BP readings expected during the 24-h period and (4) no more than two non-consecutive hours with less than one valid BP reading, and no consecutive hours with less than one valid BP reading.

Self-measured BP
Patients were provided with automated BP devices to establish self-measured BP at home three times in the morning (0700–1100 hours) and three times in the evening (2000–2300 hours) at baseline during the single-blind period (days -14 to -1) and from day 50 in the evening to day 63 in the morning during the simulated non-adherence period. Patients self-measured BP using an Omron R7 automatic wrist BP monitor (Omron Healthcare Inc., Bannockburn, IL, USA) attached to the wrist that gave the higher BP at the first patient visit; measurements were taken from the same wrist throughout the trial.

Biomarker assessments
In a subset of patients ($n = 150$), PRA (Diasorin kit; Diasorin, Stillwater, MN, USA) and PRC (Renin III generation kit; CIS Bio International, Gif sur Yvette, France) were measured by a radioimmunoassay of samples taken at baseline, day 42 (following once-daily active treatment for 6 weeks) and day 63 (following two successive simulated missed doses of treatment). Blood samples for biomarker assessments were drawn between 0700 and 1000 hours at each visit, with a maximum variation of 1 h in the time of sampling at each visit. Patients had to be in the fasting state (intake of water only) for at least 8 h before sampling, and remained in a supine position for 20 min before and during sampling; sampling was re-scheduled if patients had exercised or appeared stressed. Blood was collected into EDTA tubes at ambient temperature, and within 5 min was centrifuged for 10 min at 1300 *g* at room temperature for extraction of plasma. Plasma samples were stored at $-20\,^{\circ}$C until required for analysis.

Tolerability assessments
At the screening visit, medical and disease histories were recorded. Besides a complete physical examination, urine and laboratory tests were performed at the screening visit, the start of the active treatment period and at the end of the study (day 63). Adverse events (AEs) and concomitant medications were

assessed at regular intervals throughout the study. The safety population comprised all patients who received at least one dose of study drug and had at least one post-baseline safety assessment.

Treatment compliance
Compliance was assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the patient. Patient compliance had to be at least 80% during the single-blind placebo run-in and the active treatment period, and 100% during the simulated non-adherence period.

Data analyses
Ambulatory BP-monitoring period. The primary efficacy variable (change from baseline in 24-h MADBP) was analysed for all patients who had a successful 24-h MABP measurement at baseline and at day 42/49 (the ABPM completer population).

Comparisons between groups (aliskiren vs irbesartan and aliskiren vs ramipril) for the hourly change from baseline in 24-h MADBP were carried out using a two-way repeated-measures analysis of covariance (ANCOVA) model with treatment, country and visit of missed dose as factors, and the baseline mean value as the covariate. Least-squares mean and 95% confidence intervals (CI) for between-treatment differences were calculated for each treatment comparison.

Secondary efficacy variables were assessed in a similar manner and included the change from baseline to day 42/49 in 24-h MASBP, daytime (0600–2200 hours) MASBP/MADBP, night-time (2200–0600 hours) MASBP/MADBP. The difference between 24-h ABPM profiles after a missed dose relative to the change after an active dose on day 42/49 was also assessed using the same model.

Self-measured BP. Changes in self-measured BP after a missed dose were compared across treatment groups at 24, 36 and 48 h after the last active dose using a two-way ANCOVA model with country, treatment and day of missed dose as factors, subject as a random effect and baseline as covariate, with treatment contrasts made to compare the treatment effect on change in BP.

Self-measured BP was analysed for the intent-to-treat (ITT) population. BP readings made outside the specified time periods for morning (0700–1100 hours) and evening (2000–2300 hours) measurement were not included in the analysis.

PRA and PRC. Changes from baseline in PRA and PRC at days 42 and 63 were compared between treatment groups using an ANCOVA model on log-transformed data with treatment and country as factors and baseline as covariate. All the statistical tests were performed at a two-sided significance level of 0.05. Data were analysed by J Botha (Novartis Pharma AG, Basel, Switzerland) using SAS 8.2 (SAS Institute, Cary, NC, USA).

Results

Study population
Of the 1149 patients who entered the single-blind placebo run-in phase of the study, 654 were randomized: 218 patients to aliskiren, 222 to irbesartan and 214 to ramipril (Figure 1). The majority of patients in each group had a successful 24-h MABP measurement at baseline and at day 42/49 and were thus included in the ABPM completer population for efficacy analyses: 155 patients (71%) in the aliskiren group, 171 (77%) in the irbesartan group and 152 (71%) in the ramipril group. All randomized patients were included in the safety population.

Patient demographics and characteristics at baseline were similar between treatment groups, although there was a higher proportion of women in the ramipril group than in the aliskiren or irbesartan groups (Table 1). Baseline 24-h ambulatory and self-measured BP values were similar for each treatment group.

Ambulatory BP
Mean reductions from baseline in 24-h MADBP with aliskiren following a missed dose on day 42/49 (7.0 ± 0.4 mm Hg) were similar to those observed after a missed dose of irbesartan (7.3 ± 0.4 mm Hg; treatment difference 0.3 mm Hg; 95% CI −0.7, 1.4; $P = 0.514$) and were significantly larger than following a missed dose of ramipril (5.0 ± 0.4 mm Hg; treatment difference 2.0 mm Hg; 95% CI −3.0, −0.9; $P = 0.0004$) (Figure 2a). Mean reductions from baseline in 24-h SBP following a missed dose with aliskiren (9.3 ± 0.6 mm Hg) were also similar to irbesartan (9.5 ± 0.6 mm Hg; treatment difference 0.2 mm Hg; 95% CI −1.3, 1.8; $P = 0.768$) and significantly larger than with ramipril (7.1 ± 0.6 mm Hg; treatment difference 2.2 mm Hg; 95% CI −3.8, −0.6; $P = 0.008$).

Time curves for 24-h MABP after an active or missed dose were similar for aliskiren (Figure 2b) but showed clear separation for irbesartan (Figure 2c) and ramipril (Figure 2d). Compared with an active dose, loss of BP-lowering effect after a missed dose of treatment was significantly smaller with aliskiren than with either irbesartan or ramipril (Figures 3a and b). Changes in daytime and night-time ambulatory BP showed similar trends to the 24-h BP data. Daytime MASBP/MADBP reductions following a missed dose were similar with aliskiren (9.4/7.2 mm Hg) and irbesartan (9.9/7.5 mm Hg) and numerically greater than those observed with ramipril (7.4/5.5 mm Hg), but there were no significant differences between groups. Reductions in night-time MASBP/MADBP with aliskiren (9.0/6.3 mm Hg) were similar to irbesartan (8.6/6.5 mm Hg) and tended to be larger than

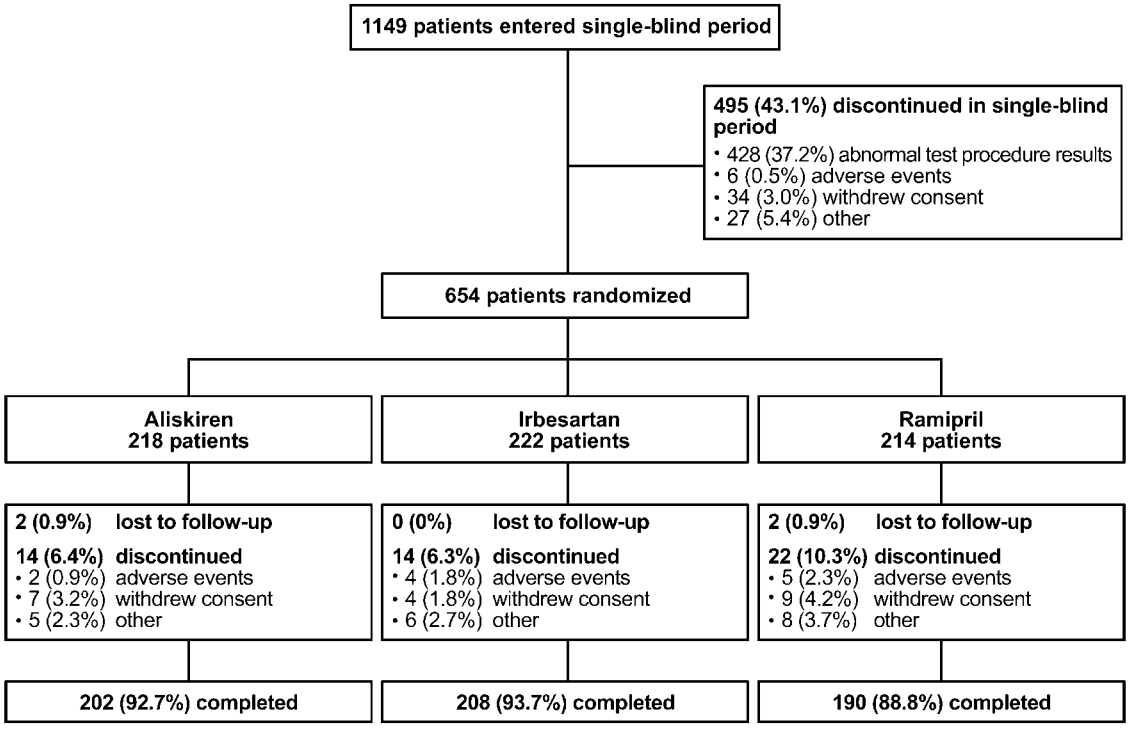

Figure 1 Patient flow diagram.

Table 1 Patient baseline and demographic characteristics (randomized population)

Characteristic	*Treatment group*		
	Aliskiren (n = *218*)	*Irbesartan* (n = *222*)	*Ramipril* (n = *214*)
Age (years)	53.5 ± 10.7	53.4 ± 9.7	53.9 ± 9.9
Female, *n* (%)	81 (37)	80 (36)	93 (44)
Race, *n (%)*			
Caucasian	209 (95.9)	217 (97.7)	210 (98.1)
Black	5 (2.3)	3 (1.4)	3 (1.4)
Asian	2 (0.9)	0	0
Other	2 (0.9)	2 (0.9)	1 (0.5)
BMI ($kg\,m^{-2}$)	28.9 ± 4.4	29.0 ± 4.6	28.9 ± 4.4
BMI $\geqslant 30\,kg\,m^{-2}$, *n* (%)	74 (33.9)	84 (37.8)	79 (36.9)
Duration of hypertension (years)	6.7 ± 5.7	7.6 ± 8.1	6.9 ± 6.6
Treatment-naive, *n* (%)	13 (6.0)	6 (2.7)	10 (4.7)
24-h MABP (mm Hg)	(*n* = 155)	(*n* = 171)	(*n* = 152)
Systolic	145.5 ± 11.0	145.4 ± 12.1	145.8 ± 13.0
Diastolic	92.9 ± 6.3	93.0 ± 6.4	92.4 ± 7.2
Self-measured BP (mm Hg)	(*n* = 208)	(*n* = 209)	(*n* = 198)
Systolic	146.0 ± 12.2	147.3 ± 14.4	146.8 ± 14.5
Diastolic	91.4 ± 7.7	92.3 ± 8.3	91.4 ± 8.0
PRA ($ng\,ml^{-1}$ per h)[a]	0.57 (*n* = 53)	0.75 (*n* = 54)	0.93 (*n* = 43)
PRC ($ng\,l^{-1}$)[a]	5.47 (*n* = 53)	6.75 (*n* = 53)	8.09 (*n* = 40)

Abbreviations: BMI, body mass index; BP, blood pressure; MABP, mean ambulatory blood pressure; PRA, plasma renin activity; PRC, plasma renin concentration. Values are arithmetic mean ± s.d. unless otherwise stated.
[a]PRA and PRC values are given as geometric means for the subset of patients with biomarker measurements.

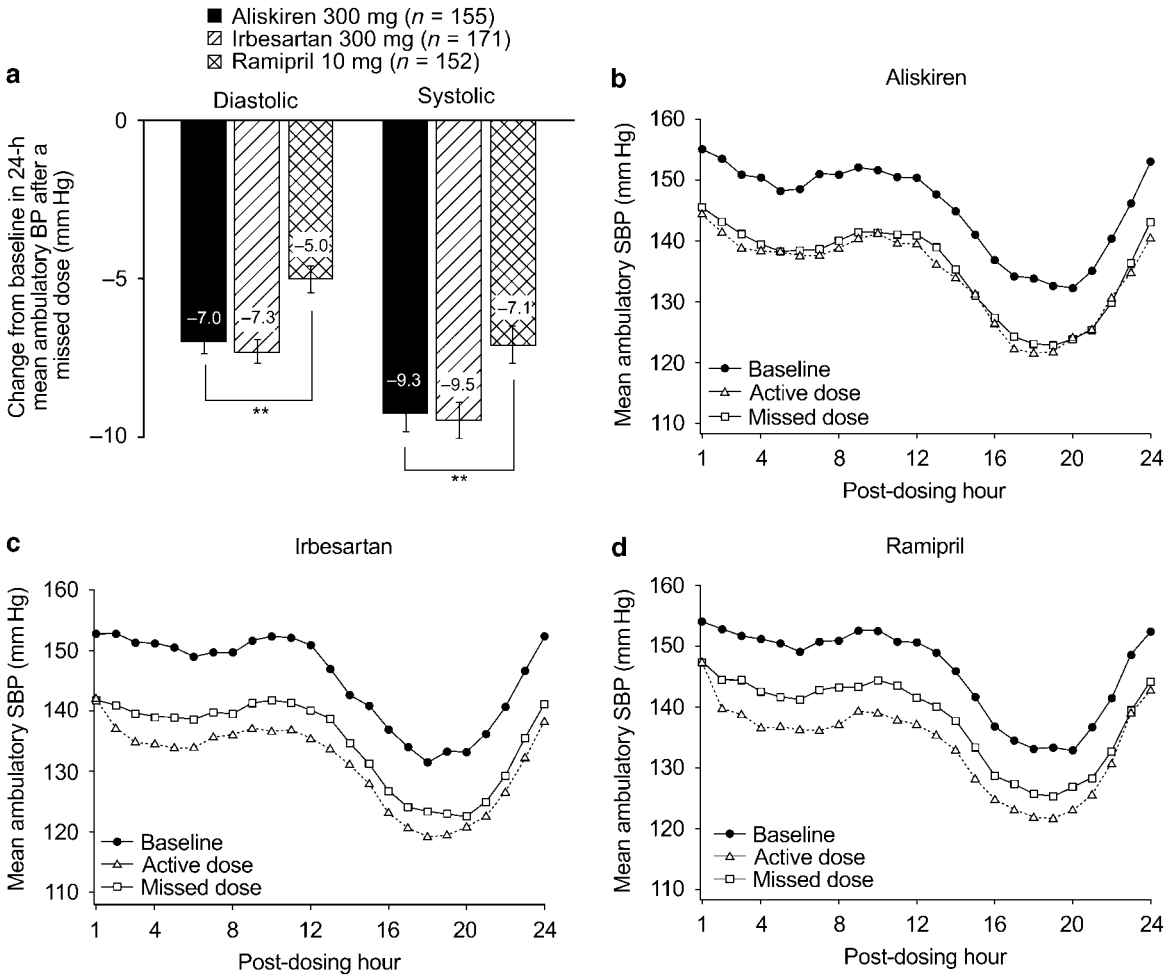

Figure 2 (**a**) Change from baseline in 24-h mean ambulatory systolic and diastolic blood pressure (BP) after a missed dose of aliskiren 300 mg, irbesartan 300 mg or ramipril 10 mg. Hourly change in 24-h mean ambulatory systolic BP at baseline, after a missed dose of treatment, and after an active dose of treatment for patients receiving (**b**) aliskiren 300 mg, (**c**) irbesartan 300 mg or (**d**) ramipril 10 mg. Values are presented as least-squares mean ± s.e.m. (**a**) or mean (**b–d**). $^{**}P<0.01$ for pair-wise comparison (analysis of covariance (ANCOVA) model). SBP, systolic blood pressure.

those with ramipril (6.3/4.4 mm Hg; $P=0.077$ for MASBP and $P=0.052$ for MADBP vs aliskiren).

Simulated non-adherence period (self-measured BP)

Baseline self-measured SBP/DBP was similar across treatment groups (Table 1). The morning measurement on day 54 (the final measurement before the first dose of placebo) showed reductions from baseline in self-measured SBP/DBP of 9.3/5.9 mm Hg with aliskiren ($n=159$), 9.7/6.4 mm Hg with irbesartan ($n=168$) and 5.8/3.1 mm Hg with ramipril ($n=141$).

During simulated non-adherence, BP control was generally better maintained (smaller increases in self-measured BP) at 24, 36 and 48 h following a missed dose with aliskiren relative to either irbesartan or ramipril (Table 2). Increases in self-measured DBP were significantly larger with irbesartan than with aliskiren after 36 and 48 h of non-adherence; SBP increases were significantly larger with ramipril after 24 h and with irbesartan after 36 h.

PRA and PRC

Baseline geometric mean PRA was 0.57, 0.75 and 0.93 ng ml^{-1} per hour, respectively, in the aliskiren ($n=53$), irbesartan ($n=54$) and ramipril ($n=43$) groups. Aliskiren reduced PRA by 58% from baseline at day 42, and this effect was maintained at day 63 (63% reduction from baseline). Irbesartan and ramipril increased PRA by 205 and 36%, respectively, at day 42 (both $P<0.0001$ vs aliskiren), but the effect of both drugs was reduced at day 63 (40 and 9% increase, respectively, in PRA from baseline). At day 42, PRC increased from baseline by 286% with aliskiren, 162% with irbesartan and 1% with ramipril (data not shown).

Tolerability

All study treatments were generally well tolerated. AEs were reported for a similar proportion of patients in each treatment group (Table 3) and the majority were mild or moderate in severity. The most common individual AEs were headache,

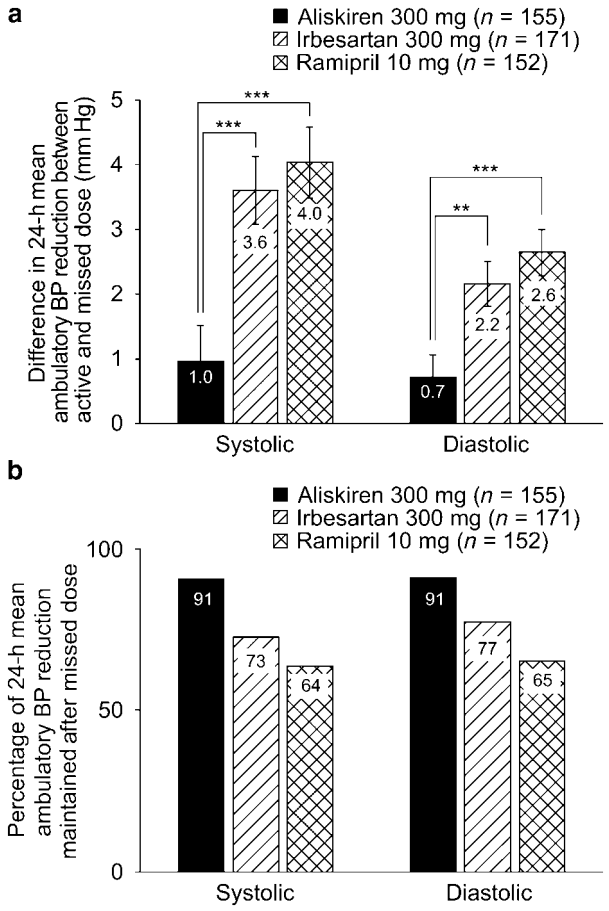

Figure 3 (**a**) Difference in 24-h mean ambulatory systolic and diastolic blood pressure (BP) between active and missed doses of aliskiren 300 mg, irbesartan 300 mg or ramipril 10 mg, and (**b**) percent of 24-h mean ambulatory BP reduction maintained after a missed dose of each treatment. Values are presented as least-squares mean ± s.e.m. (**a**) and percentage of active dose BP reduction maintained (**b**). $^{**}P<0.01$, $^{***}P<0.001$ for pair-wise comparisons (analysis of covariance (ANCOVA) model).

influenza-like symptoms and cough. The rates of headache and influenza were similar among treatment groups, but cough was reported by a larger proportion of patients receiving ramipril (6.1%) compared with aliskiren (0.5%) or irbesartan (1.8%). The rates of discontinuation due to AEs were low; cough was the only AE that led to treatment discontinuation in more than one patient (four patients: three on ramipril and one on irbesartan).

There were no deaths during the study. Six serious AEs occurred, one each in the aliskiren (asthmatic crisis) and ramipril (hypertensive crisis) groups, and four in the irbesartan group (angina pectoris, hepatitis alcoholic, renal colic and vestibular neuronitis). None was judged by the investigator to be related to the study drug.

Changes from baseline in laboratory biochemistry and haematology parameters were small, and there were no clinically meaningful differences between the treatment groups. The incidence of serum potassium levels <3.5 or $>5.5\,\mathrm{mmol\,l^{-1}}$ was low and was similar in all groups. One patient receiving irbesartan exhibited a potassium level $\geqslant 6.0\,\mathrm{mmol\,l^{-1}}$ and one patient in the ramipril group exhibited blood urea nitrogen $>14.28\,\mathrm{mmol\,l^{-1}}$.

Discussion

Despite careful monitoring and active attempts to improve adherence, even patients who are otherwise persistent with taking their antihypertensive medication will occasionally miss a dose of treatment.[4] Thus, antihypertensive treatment that provides sustained BP-lowering efficacy beyond the 24-h dosing interval is of considerable clinical importance. This study shows that the direct renin inhibitor aliskiren 300 mg provides significant reductions from baseline in 24-h ambulatory BP. In the 24-h period after a simulated missed dose (that is, 24–48 h after an active dose), aliskiren maintained almost all (91% of 24-h MASBP/MADBP reduction) of the 24-h BP control obtained following an active dose. Although reductions in 24-h MABP following an active dose were larger with irbesartan 300 mg than with aliskiren 300 mg, patients who missed a dose of irbesartan lost approximately one-quarter of the BP-lowering effect (73/77% of 24-h MASBP/MADBP reduction maintained) during the 24–48-h period after dose, such that the mean reduction from baseline in 24-h ambulatory BP was similar to that observed with aliskiren. Ramipril 10 mg lowered 24-h ambulatory BP to the same extent as did aliskiren after an active dose, but patients who missed a dose of ramipril lost about one-third of the BP-lowering effect in the same period (64/65% of 24-h MASBP/MADBP reduction maintained). Biomarker assessments indicate that aliskiren also maintained inhibition of renin system activity (reduction in PRA) for at least 48 h following a missed dose. All three treatments were generally well tolerated, although, as expected, ramipril was associated with an increased incidence of cough.

This is the first study to compare the BP-lowering effect of aliskiren in the 24–48-h post-dose period with that of other commonly used antihypertensive agents. The small loss in ambulatory BP-lowering effect of 1.0/0.7 mm Hg with aliskiren in the 24–48-h period relative to the 0–24-h period compares favourably not only with that observed with irbesartan (3.6/2.2 mm Hg) or ramipril (4.0/2.6 mm Hg) in this study, but also with that observed with other antihypertensive drugs in previous studies.[10–13] Although comparisons across different studies must be interpreted with caution, the only other study that has reported a $\leqslant 1$ mm Hg loss of 24-h ambulatory SBP/DBP-lowering effect in the 24–48-h post-dose period relative to the 0–24-h period involved amlodipine,[10] an agent well known for its long duration of action. This study also used a simulated non-adherence phase, involving morning and evening self-measurement of BP by patients at home, to

Table 2 Change in mean self-measured BP from the morning of the first missed dose to 24, 36 and 48 h after the missed dose (simulated non-adherence phase; ITT population)

Time after start of simulated non-adherence	*Self-measured blood pressure (mm Hg)*		
	Aliskiren	*Irbesartan*	*Ramipril*
Baseline			
SBP, mm Hg (day 54 AM)	137.2 ± 17.1	137.5 ± 17.7	142.3 ± 16.9
SBP, mm Hg (day 61 AM)	137.6 ± 16.7	139.2 ± 18.4	139.8 ± 19.4
DBP, mm Hg (day 54 AM)	86.3 ± 11.4	86.3 ± 11.6	89.3 ± 11.5
DBP, mm Hg (day 61 AM)	86.8 ± 11.3	86.2 ± 11.0	87.1 ± 9.8
24 h			
SBP, mm Hg (day 55 AM)	137.6 ± 16.8	139.0 ± 17.1	144.2 ± 18.7
SBP, mm Hg (day 62 AM)	138.7 ± 16.2	140.2 ± 17.2	142.6 ± 18.0
ΔSBP	+1.7 ± 1.3 (n = 179)	+3.0 ± 1.3 (n = 178)	+5.7 ± 1.4* (n = 165)
DBP, mm Hg (day 55 AM)	87.2 ± 12.3	86.6 ± 10.8	90.0 ± 12.1
DBP, mm Hg (day 62 AM)	87.2 ± 10.4	87.1 ± 10.6	89.2 ± 10.5
ΔDBP	+1.7 ± 0.9 (n = 179)	+2.1 ± 0.9 (n = 178)	+3.4 ± 1.0 (n = 165)
36 h			
SBP, mm Hg (day 55 PM)	135.8 ± 17.2	141.0 ± 19.6	140.9 ± 16.4
SBP, mm Hg (day 62 PM)	138.8 ± 17.8	141.5 ± 19.6	140.8 ± 18.3
ΔSBP	+1.3 ± 1.6 (n = 158)	+6.5 ± 1.6* (n = 160)	+3.0 ± 1.7 (n = 147)
DBP, mm Hg (day 55 PM)	84.4 ± 11.7	87.0 ± 12.3	86.7 ± 10.9
DBP, mm Hg (day 62 PM)	86.0 ± 11.9	86.6 ± 11.7	86.2 ± 11.5
ΔDBP	−0.3 ± 1.1 (n = 158)	+3.3 ± 1.1* (n = 160)	+0.0 ± 1.2 (n = 147)
48 h			
SBP, mm Hg (day 56 AM)	139.2 ± 18.6	140.7 ± 17.6	143.1 ± 17.8
SBP, mm Hg (day 63 AM)	138.9 ± 18.1	139.7 ± 16.5	142.1 ± 20.6
ΔSBP	+4.3 ± 1.6 (n = 142)	+4.9 ± 1.6 (n = 139)	+4.0 ± 1.7 (n = 135)
DBP, mm Hg (day 56 AM)	87.1 ± 12.7	88.7 ± 11.7	88.9 ± 11.5
DBP, mm Hg (day 63 AM)	86.8 ± 11.5	88.8 ± 11.1	88.4 ± 12.0
ΔDBP	+1.7 ± 1.1 (n = 142)	+5.8 ± 1.1** (n = 139)	+2.2 ± 1.1 (n = 135)

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure. SBP and DBP are mean ± s.d. self-measured BP values at each time point after a missed dose (simulated non-adherence). ΔSBP and ΔDBP are least-squares mean ± s.e.m. changes from baseline.
*P < 0.05, **P < 0.01 vs aliskiren.

evaluate BP-lowering effects up to 72 h after dose (that is, following two successive simulated missed doses of treatment). Although the self-measured BP data showed greater variability than the 24-h MABP data, the overall results showed a similar trend towards better maintenance of BP control (that is, smaller increases in BP) up to 72 h after an active dose with aliskiren than with irbesartan or ramipril. Ramipril clearly provided the least durable effect of the three drugs, and this study suggests that ramipril 10 mg once daily does not provide effective BP reduction beyond 24 h after dosing. These results are consistent with the finding of a small randomized, crossover study that ambulatory DBP reductions with ramipril 10 mg once daily wane 19–22 h after dosing.[14]

Biomarker measurements in this study confirm that aliskiren provides sustained reductions in PRA and elevations in PRC following one or two missed doses (that is, for at least 72 h after dose). The study design allowed for comparison of effects of treatments on PRA and PRC at 24 h after dose (day 42 measurement) and 72 h after dose (day 63 measurement, following placebo doses on days 61 and 62). Reduction in PRA is a direct measure of renin system inhibition, and an indirect measure of the effect of ACE inhibitors and ARBs to prevent the formation or action of angiotensin (Ang) II, respectively (as this stimulates a reactive rise in PRA through the short feedback loop[15]). Our results show that renin system inhibition provided by active treatment with aliskiren 300 mg (day 42, 58% reduction in PRA) was fully maintained 72 h after dosing (day 63, 63% reduction in PRA). By contrast, the increase in PRA stimulated by Ang II receptor blockade with irbesartan 300 mg (day 42, 205% increase) diminished by more than 80% at 72 h after dose (day 63, 40% increase). Changes in PRC similarly showed that the effect of aliskiren to inhibit the renin system was maintained better than the effect of irbesartan. Ramipril 10 mg was associated with small increases in trough PRA and no

Table 3 Tolerability of study treatments (safety population)

	Treatment group		
	Aliskiren (n = *218*)	*Irbesartan* (n = *222*)	*Ramipril* (n = *214*)
Any adverse event	77 (35.3)	73 (32.9)	77 (36.0)
Discontinuations due to adverse events	2 (0.9)	3 (1.4)	4 (1.9)
Serious adverse events	1 (0.5)	4 (1.8)	1 (0.5)
Adverse events reported by ⩾2% of patients in any treatment group			
Headache	12 (5.5)	13 (5.9)	15 (7.0)
Influenza-like symptoms	8 (3.7)	6 (2.7)	5 (2.3)
Cough	1 (0.5)	4 (1.8)	13 (6.1)
Dizziness	4 (1.8)	6 (2.7)	8 (3.7)
Nasopharyngitis	5 (2.3)	4 (1.8)	4 (1.9)
Asthenia	2 (0.9)	5 (2.3)	4 (1.9)
Diarrhoea	3 (1.4)	1 (0.5)	6 (2.8)
Dyspepsia	1 (0.5)	5 (2.3)	3 (1.4)
Gastroenteritis	2 (0.9)	1 (0.5)	5 (2.3)
Clinically notable changes in laboratory values			
BUN $>14.28\,mmol\,l^{-1}$	0	0	1/213 (0.5)
Creatinine $>176.8\,\mu mol\,l^{-1}$	0	0	0
Potassium			
$<3.5\,mmol\,l^{-1}$	5/217 (2.3)	2/221 (0.9)	5/213 (2.3)
$>5.5\,mmol\,l^{-1}$	6/217 (2.8)	3/221 (1.4)	4/213 (1.9)
$\geqslant 6.0\,mmol\,l^{-1}$	0	1/221 (0.5)	0

Abbreviation: BUN, blood urea nitrogen.
Values are presented as the number (%) of patients.

significant changes in PRC at days 42 and 63. The lack of effect of ramipril on PRC at 24 h after dose is inconsistent with findings from previous studies with ramipril 10 mg,[9,16] and may be a chance finding related to the relatively small number of patients who underwent biomarker assessments in the ramipril group.

Previous studies have shown that the BP-lowering effects of aliskiren last beyond the 24-h dosing interval in patients with hypertension. In a randomized, double-blind, dose-finding study, 608 patients who completed 8 weeks of treatment with aliskiren monotherapy entered a 2-week withdrawal period.[8] Office BP reduction from baseline with aliskiren 300 mg was 14.7/11.1 mm Hg at week 8. BP increased only gradually after stopping aliskiren treatment, and remained 11.6/9.5 mm Hg below baseline at 4 days after stopping treatment (that is, 80% of the BP-lowering effect was maintained); a 64.7% reduction from baseline in PRA also persisted 2 weeks after the last dose.[8] Similarly, in a 4-week, placebo-controlled withdrawal period initiated by 675 patients who had completed a 6-month, double-blind comparator study of aliskiren- and ramipril-based therapy, office BP increased more rapidly after stopping ramipril- than aliskiren-based therapy. Median BP exceeded 140/90 mm Hg 1 week after stopping ramipril, but 4 weeks after stopping aliskiren.[9]

The long duration of action of aliskiren in part reflects its long terminal elimination half-life (approximately 40 h)[6] and high potency for inhibition of human renin (IC_{50} 0.6 $nmol\,l^{-1}$).[17] Calculations of the stoichiometry of aliskiren to renin molecules during aliskiren treatment predict the sustained inhibition of PRA (and consequent BP-lowering effects) by aliskiren beyond the 24-h dosing interval.[18]

All study treatments were generally well tolerated, although, as would be expected for an ACE inhibitor, ramipril treatment was associated with a higher incidence of cough than either aliskiren or irbesartan. Elevations of serum potassium $>5.5\,mmol\,l^{-1}$ were infrequent, and elevation to $\geqslant 6.0\,mmol\,l^{-1}$ was observed in only one patient (receiving irbesartan).

In conclusion, aliskiren 300 mg provided sustained BP-lowering effects beyond 24 h that were longer lasting than with irbesartan 300 mg or ramipril 10 mg, and was generally well tolerated. Aliskiren may therefore represent an important new option for the treatment of patients with hypertension, in whom occasional non-adherence is common.

Conflict of interest

PP has received honoraria from Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA. WJ and ES report no conflicts of interest. JB, CB and DLK are employees of Novartis Pharmaceuticals Corporation and are thus eligible for Novartis stock and stock options.

What is known about this topic

- Most patients with hypertension inadvertently miss an occasional dose of antihypertensive drug treatment (that is, exhibit occasional non-adherence).
- Sustained BP control throughout the 24-h dosing interval is required for effective reduction in cardiovascular risk, and this would be lost during periods of non-adherence. Agents that provide sustained BP reduction beyond the 24-h dosing interval are therefore desirable.
- The direct renin inhibitor aliskiren exhibits a long terminal elimination half-life of approximately 40 h and has demonstrated effective BP control over the 24-h dosing interval and after stopping treatment in patients with hypertension.

What this study adds

- Aliskiren 300 mg provided sustained BP-lowering effects beyond 24 h that were longer lasting than with irbesartan 300 mg or ramipril 10 mg. Significantly more of the systolic BP-lowering effect of aliskiren was maintained in the 24 h after a missed dose (91%) compared with irbesartan (73%; $P<0.01$) or ramipril (64%; $P<0.0001$).
- Aliskiren provided sustained reduction in plasma renin activity (PRA) following one or two missed doses (that is, for at least 72 h after dose).
- Aliskiren may represent an important new option for the treatment of patients with hypertension, in whom occasional non-adherence is common.

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PP, WJ and ES participated in the writing of the study protocol, approved the final protocol, participated in the collection, analysis and interpretation of data as well as in the writing of the paper, and also approved the final paper. JB, CB and DLK participated in the design of the study and in the writing of the study protocol, approved the final protocol, supported the undertaking of the study, participated in the analysis and interpretation of the data as well as in the writing of the paper, and also approved the final paper. The authors take full responsibility for the content of the paper but thank Dr Richard White (Oxford PharmaGenesis™ Ltd) for assistance in collating the comments of the authors and editing the final paper. This work was funded by Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA.

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Appendix

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