Original Article

Sustained decrease in blood pressure following missed doses of aliskiren or telmisartan: the ASSERTIVE double-blind, randomized study

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Objectives: The AliSkiren Study of profound antihypERtensive efficacy in hyperTensIVE patients (ASSERTIVE) study was designed to assess the sustained blood pressure (BP)-lowering effect of aliskiren vs. telmisartan after a 7-day treatment withdrawal in patients with hypertension.

Methods: Patients were randomized to once-daily aliskiren 150 mg ($N = 414$) or telmisartan 40 mg ($N = 408$). After 2 weeks, all patients were uptitrated to double the initial dose for 10 weeks; subsequently, all patients were treated with placebo to simulate a 7-day treatment withdrawal.

Results: At the end of active treatment (EoA), similar decreases in mean ambulatory BP were observed with aliskiren and telmisartan. From EoA to day 7 of treatment withdrawal (end of withdrawal, EoW), the least squares mean increase in 24-h mean ambulatory SBP was smaller for aliskiren (2.7 mmHg) vs. telmisartan (6.5 mmHg). Between-treatment difference was significant in favour of aliskiren (−3.8 mmHg; $P < 0.0001$). Similar effects were observed for the increase in 24-h mean ambulatory DBP after EoW (−2.1 mmHg; $P < 0.0001$). Mean sitting SBP and DBP were also significantly lower with aliskiren than telmisartan after EoW with SBP (2.0 mmHg) and DBP (1.1 mmHg) differences in favour of aliskiren, already evident on day 2 after a single 'missed dose'.

Conclusion: Aliskiren showed a greater and more sustained BP-lowering effect than telmisartan during a 7-day treatment withdrawal. Aliskiren may provide sustained BP lowering during 1 day or more missed dose.

Keywords: aliskiren, ambulatory blood pressure, angiotensin receptor blocker, antihypertensive therapy, blood pressure variability, direct renin inhibitor, drug holiday, telmisartan

Abbreviations: ABPM, ambulatory blood pressure monitoring; ARB, angiotensin receptor blocker; CI, confidence interval; EoA, end of active treatment; EoW, end of withdrawal; Geo-mean, geometric mean; LSM, least squares mean; MABP, mean ambulatory BP; MADBP, mean ambulatory DBP; MASBP, mean ambulatory SBP; msSBP, mean sitting SBP; msDBP, mean sitting DBP; PRA, plasma renin activity; PRC, plasma renin concentration; RAAS, renin–angiotensin–aldosterone system; RAN, randomization; SAE, serious adverse event

INTRODUCTION

Management of chronic diseases is often challenged by patients' long-term adherence to taking prescription medicines. Missed doses of antihypertensive medication may limit their clinical effectiveness, leading to inadequate control of blood pressure (BP) and a consequent increase in the risk of cardiovascular events, especially in patients with comorbidities such as diabetes [1–5].

Various studies have investigated the sustained efficacy of different therapies and the implications of missed doses [6–15]. A longitudinal database study showed that patients who are prescribed a once-daily dose of antihypertensive medication frequently miss doses [16]. It was observed that 42% of all missed doses were single-day omissions, 15% were 2-day omissions and the remaining 43% were sequences of three or more consecutive omissions. Depending on the medication's duration of action, the efficacy of antihypertensive therapy reduces over the missed dose period [17,18]. Although the medical community is increasingly paying attention to patient education on regimen adherence, it remains an unmet target. Immediate and significant results may be achieved, however, by selecting antihypertensive drugs that provide sustained efficacy such that dose omissions are not associated with large fluctuations in BP even after nonoptimal adherence. Such drugs are also referred to as 'forgiving' drugs in the sense that consequences of missed doses are buffered.

Aliskiren and telmisartan are two established antihypertensive drugs that act on the renin–angiotensin–aldosterone system (RAAS), albeit via different mechanisms. Previous data on aliskiren, which directly inhibits the RAAS cascade at the point of its activation, indicate that aliskiren provides effective as well as sustained BP reductions over and beyond 24 h [19–21]. The sustained

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efficacy of aliskiren is largely attributed to its long half-life (approximately 40 h) and tissue distribution [22]. Telmisartan is the longest acting (half-life of approximately 24 h) angiotensin receptor blocker (ARB) that blocks the RAAS cascade downstream of renin [23]. Telmisartan is considered particularly effective at sustaining 24-h BP control, especially during the last few hours of the dosing interval when the efficacy of many once-daily antihypertensive medications wanes [24].

As both aliskiren and telmisartan have demonstrated sustained BP-lowering efficacy over a 24-h dosing period, the AliSkiren Study of profound antihypERtensive efficacy in hyperTensIVE patients (ASSERTIVE) directly compared the forgiveness offered by these drugs over a 7-day period of consecutive treatment withdrawal following 12 weeks of active treatment to simulate trends of patient nonadherence to antihypertensive therapy.

METHODS

Patients

The trial included women and men 18 years and older with a diagnosis of essential hypertension (grades 1–2) who met both of the following BP criteria at randomization (RAN): office SBP at least 140 mmHg and less than 180 mmHg and 24-h mean ambulatory SBP (MASBP) at least 135 mmHg. Major exclusion criteria included the following: severe hypertension [mean sitting SBP (msSBP) $\geq$180 mmHg and/or mean sitting DBP (msDBP) $\geq$110 mmHg], history or evidence of secondary hypertension, known Keith–Wagener grade III or IV hypertensive retinopathy, type 1 diabetes mellitus and uncontrolled type 2 diabetes mellitus defined on the basis of an investigator-initiated therapy change (patients were required to be on stable antidiabetic medications for at least 4 weeks prior to screening). Pregnant or nursing women were also excluded. Women of childbearing potential were required to use effective contraceptive methods for inclusion in the trial.

The trial was conducted in accordance with the ethical principles of the Declaration of Helsinki and the US Code of Federal Regulations (part 46, protection of human subjects) and in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice. The trial protocol was reviewed and approved by the relevant Independent Ethics Committees for each centre. The trial is registered as EudraCT number 2008–007831–41 and on ClinicalTrials.gov under the code NCT00865020. Written informed consent was obtained from each patient before participating in any trial procedures.

Study design

This was a randomized, double-blind, double-dummy, parallel group study conducted at 111 centres in 15 countries: Canada, Ecuador, Germany, Hungary, Malaysia, Mexico, Panama, Philippines, Republic of Korea, Singapore, Slovakia, Spain, Turkey, the UK and Venezuela. Following a 2-week washout and 1–2-week placebo run-in period, patients were randomized to 12 weeks of double-blind active treatment with either once-daily aliskiren or telmisartan (force titration to double the initial doses after 2 weeks of active treatment). Following this, both treatments were replaced with placebo, and the primary efficacy analyses were carried out after 2 and 7 days of treatment withdrawal. The overall study was, thus, divided into three phases: a washout and placebo period, an active treatment period, and an active treatment withdrawal period with placebo, as shown in Fig. 1 and described in more details below.

Antihypertensive washout and placebo run-in period

After the screening visit, eligible patients entered a 2-week washout period (if receiving antihypertensive medication), followed by a placebo run-in period of 1–2 weeks. Patients not receiving any antihypertensive treatment for at least 2 weeks at the time of the screening visit directly entered the 1–2-week placebo run-in period. Patients with office SBP of at least 180 mmHg or DBP of at least 110 mmHg were withdrawn from the study; all patients were telemonitored with BP device (A&D UA 767-BT; Medical/LifeSource, San Jose, California, USA), and automatic alerts were sent to investigators when predefined thresholds were exceeded (Core Lab Partners Ltd, Rockville, Maryland, USA). After the placebo run-in period, eligible patients were randomized (1 : 1 ratio) to once-daily aliskiren 150 mg or telmisartan 40 mg.

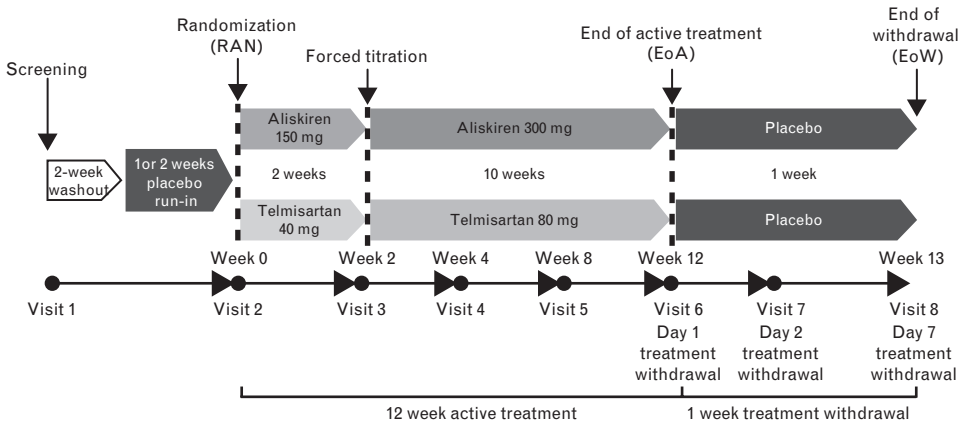

FIGURE 1 Study design.

Double-blind, active-controlled treatment period

After 2 weeks of double-blind, active treatment, initial doses were force titrated to double the dose for a further 10 weeks (i.e. aliskiren 300 mg and telmisartan 80 mg). Patients were instructed to take study medication at approximately 0800 h every day, except on the day of a study visit when it was taken after diagnostic procedures.

Treatment withdrawal period

At the end of the 12-week active treatment (EoA) period, all patients received placebo for a 1-week treatment withdrawal period. During this period, patients' BP was monitored remotely as indicated before.

STUDY OBJECTIVES

Treatment efficacy was evaluated over two periods that were defined as follows (Fig. 1): from RAN to the EoA period and from the EoA period to day 7 of the treatment withdrawal period [EoA to end of withdrawal (EoW)].

The period for the primary endpoint was EoA to EoW. The primary objective was to compare the sustained efficacy of aliskiren 300 mg with that of telmisartan 80 mg based on the increase in 24-h MASBP following treatment withdrawal, that is, from EoA to EoW, to assess the 'degree of forgiveness' of these two drugs. A post-hoc analysis to evaluate the percentage of patients in each treatment arm who had a similar change in 24-h MASBP from EoA to EoW was also conducted. Subcuts of 4 mmHg were used for this analysis.

Secondary objectives included analogous comparison of the changes in 24-h mean ambulatory DBP (MADBP) from EoA to EoW and comparisons of MASBP and MADBP from RAN to EoA. Changes in office BP were evaluated from RAN to EoA, EoA to 48 h after the last active dose (day 2) and EoA to EoW. Changes from EoA to EoW and RAN to EoA for circadian variation in mean ambulatory BP (MABP) and office BP were also evaluated. Additionally, the overall safety and tolerability of aliskiren and telmisartan was monitored and recorded throughout the study.

Exploratory objectives included assessment of the biomarkers plasma aldosterone, plasma renin activity (PRA) and plasma renin concentration (PRC). In addition, a post-hoc analysis was conducted to assess BP changes (MABP and office BP) from EoA to EoW and RAN to EoA in the subgroup of patients with concomitant diabetes.

STUDY ASSESSMENTS

Efficacy assessments

Ambulatory blood pressure monitoring

MABP was assessed over 24 h at RAN (week 0), at week 12 (EoA) after patients had received double-blind active treatment and at week 13 (EoW) after patients had received placebo. If the measurement of MABP was not meeting standard validity criteria at RAN, a repeat measurement was permitted within 24–72 h, provided the patient continued to receive placebo. Repeat ABP monitoring (ABPM) was not permitted at EoA or EoW. ABPM setup and calibration was performed between 0700 and 1000 h using a SpaceLabs 90207 oscillometric device (SpaceLabs Medical Inc., Redmond, Washington, USA) applied to the nondominant arm of the patient. Validity criteria for ABPM measurements included a minimum test duration of 24 h, at least 70% of valid expected BP measurements in the 24 h, no more than two nonconsecutive hours missing and no consecutive hours without one reading. Quality control criteria for ABPM recordings were evaluated automatically by WebHeart ABPM software, and were managed independently by a third-party provider (Core Lab Partners Ltd, Princeton, New Jersey, USA).

Office blood pressure measurements

Office BP was measured at screening, RAN (week 0), during the active treatment period at weeks 2, 4, 8 and 12 and on days 2 (48 h after the last active dose) and 7 (EoW) of the treatment withdrawal period. A validated and automated BP monitor (Omron HEM-705 BP monitor; J. Hewitt LLC, California, USA) with an appropriate cuff size was used for measurement of BP according to Guidelines of the British Hypertension Society [25]. Briefly, the cuff device was applied on the nondominant arm or the arm with the higher reading if there was a clinically relevant difference (SBP $\geq$ 10 mmHg and/or DBP $\geq$ 5 mmHg) between arms at the first study visit. Three sitting BP measurements were taken at 1–2-min intervals after the patient had been sitting for 5 min. The mean of these readings was calculated.

Biomarker assessments

Blood samples were collected from a subset of patients at RAN, EoA and EoW after a fast of at least 8 h. Patients were seated a minimum of 10 min prior to phlebotomy. RAN samples were collected between 0700 and 1000 h and subsequently within 1 h of the RAN collection time to minimize diurnal variation. EDTA samples were centrifuged within 5 min of collection and plasma was immediately frozen at -20°C for a maximum of 4 weeks, and then at -80°C at the central laboratory (Eurofins, Breda, The Netherlands) until assayed using complete patient sets. The biomarker, PRC was assessed using RIA Renin III kits from CISbio International (Gif-sur-Yvette, France), PRA was assessed using RIA kits from DiaSorin (Stillwater, Minnesota, USA) and aldosterone using RIA Coat-a-Count kits from Siemens (Deerfield, Illinois, USA). The biomarker data were kept blinded until the end of the study.

Safety and tolerability assessments

Adverse events and serious adverse events (SAEs) were recorded at each study visit with the investigator's assessment of relationship to study drug. Laboratory values for haematology and blood chemistry were monitored at regular intervals during the study. Vital signs were also monitored throughout the study.

To ensure safety of all patients enrolled in the study, patients were provided with an automated BP cuff device (A&D UA 767-BT; Medical/LifeSource) and were required to measure their BP at home, twice daily, during study periods without active treatment or study medication titration. Data were automatically uploaded to a third-party central database for safety monitoring, and notifications

were sent to investigators if predefined thresholds, for high or low BP, were exceeded (Core Lab Partners Ltd).

Statistical analyses

The study aimed at randomizing a total of 790 patients to have a sample size of at least 592 patients to complete the study, so as to provide 80% power for the superiority test at a two-sided significance level of 0.05. Patients were analysed according to the treatment group they were assigned to at RAN.

Randomization to study treatment was carried out using a validated system that automated the random assignment of treatment arms to randomization numbers (Almac Group Ltd, Craigavon, UK). The randomization scheme was reviewed by the Biostatistics Quality Assurance group at Novartis (Novartis Pharma AG, Basel, Switzerland) and locked by them after approval. A double-dummy design was employed to ensure adequate study blinding.

The primary efficacy endpoint was the change in 24-h MASBP between EoA and EoW and was analysed for all patients with available 24-h MABP measurement at both time points (ABPM completer set). The primary efficacy endpoint was assessed using a two-way analysis of variance (ANOVA) model with treatment and region as factors. The robustness of the primary analysis was assessed by supportive analysis using the per-protocol set (PPS).

The secondary efficacy endpoints were summarized descriptively and between-treatment comparisons were carried with an ANOVA model similar to the primary analysis method for EoA to EoW and with a two-way analysis of covariance model for RAN to EoA or EoW, using the full analysis set (including all patients to whom study treatment had been assigned and who took at least one dose of study medication). The change from EoA in MASBP, MADBP and office BP was analysed at the time point of interest with ANOVA model with treatment and region as factors. From post-hoc analysis, the subgroup of patients with diabetes was analysed with similar methods. For plasma aldosterone, PRA and PRC geometric means (Geo-means) and corresponding 95% confidence intervals were calculated. Standard descriptive analyses were employed for safety parameters. The safety population consisted of all patients who received at least one dose of study medication. All statistical analyses were performed using SAS software version 9.1 or higher (SAS Institute Inc., Cary, North Carolina, USA).

RESULTS

Patient disposition

Of 1359 patients who entered the placebo run-in period, 822 patients were randomized: 414 to aliskiren and 408 to telmisartan (Fig. 2). In total, 722 patients completed the study (12 weeks of active treatment with 7-day treatment withdrawal), 365 (88.2%) in the aliskiren and 357 (87.5%) in the telmisartan group. Major protocol deviations leading

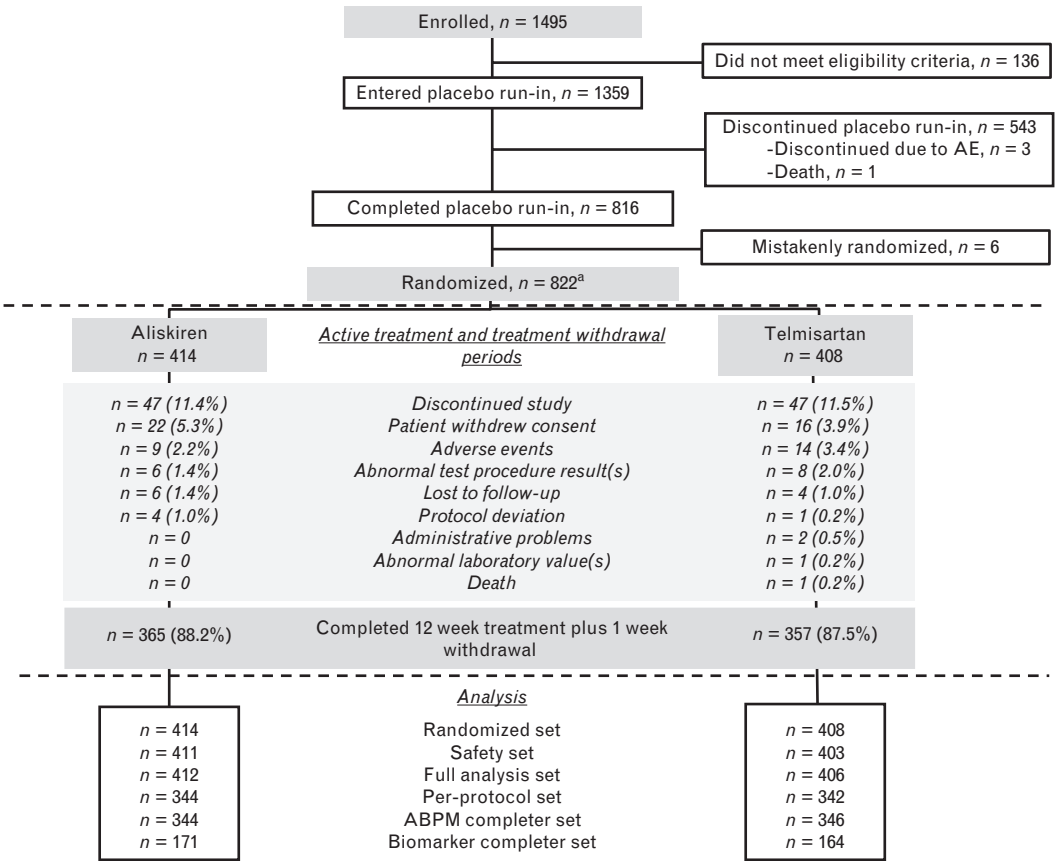

FIGURE 2 Patients Disposition. [a]There were six patients (two in the aliskiren group, four in the telmisartan group) who had a randomization number but discontinued from placebo run-in period.

to exclusion from the PPS were reported by a total of 49 (6.0%) patients: 28 (6.8%) in the aliskiren vs. 21 (5.1%) in the telmisartan group. The most commonly reported major protocol deviations were 24-h MASBP less than 135 mmHg at baseline in a total of 31 (3.8%) patients and msSBP out of range (<140 or ≥180 mmHg) or missing at baseline in a total of 11 (1.3%) patients.

Demographic and baseline characteristics

Demographic and baseline characteristics were generally comparable for the aliskiren and telmisartan treatment groups at RAN (Table 1). Most patients were whites (55.0%), although the study also included a large number of patients from Asia (23.8%). Overall, about one-third of the population was obese (BMI $\geq 30\,kg/m^2$) and 12.4% ($n = 102$) of the patients had concomitant diabetes. The mean age of patients was 56 years, and 24% patients were at least 65 years of age. The patients had a mean duration (±SD) of hypertension of 7.4 ± 6.98 years. The majority of patients (94.5%) had an estimated glomerular filtration rate of at least 60 ml/min per 1.73 m^2 at baseline.

Mean values for 24-h MASBP and MADBP and office BP (msSBP and msDBP) at RAN were similar for both treatment groups (Table 1).

Efficacy

Change in 24-h mean ambulatory SBP

Change in 24-h MASBP from EoA to EoW was the primary efficacy variable for this study. During this period, an increase in 24-h MASBP was observed with both treatments, the least squares mean (LSM) change (±SEM) being significantly higher in the telmisartan (6.5 ± 0.461 mmHg) than in the aliskiren (2.7 ± 0.466 mmHg) treatment group (LSM between-treatment difference: −3.8 mmHg, $P < 0.0001$ in favour of aliskiren; Table 2). Comparable differences were observed in the PPS confirming the robustness of the results observed in the ABPM completer set.

Both aliskiren (-11.2 ± 11.06 mmHg) and telmisartan (-12.5 ± 10.83 mmHg) provided clinically significant and similar reductions in MASBP (±SD) from RAN to EoA (Table 3) in this mild-to-moderate hypertensive population reaching a final MASBP level of 134.7 ± 11.22 and 134.6 ± 12.72 mmHg, respectively. However, when considering the complete study period from RAN to EoW, the overall reduction in MASBP was significantly better with aliskiren compared with telmisartan treatment, the LSM difference between the two treatments (±SEM) being -2.8 ± 0.736 mmHg ($P < 0.001$).

A higher percentage of patients receiving aliskiren treatment had a reduction or relatively no change in BP as compared with patients receiving telmisartan, between EoA and EoW (Supplementary Figure 1, http://links.lww.com/HJH/A161).

Change in 24-h mean ambulatory DBP

An increase in 24-h MADBP (±SEM) between EoA and EoW was observed with both treatment groups which was significantly higher in the telmisartan group (4.2 ± 0.324 mmHg) than in the aliskiren group (2.1 ± 0.328 mmHg, LSM difference of −2.1 mmHg, $P < 0.0001$) (Table 2). For the complete study period (RAN to EoW), MADBP reduction was significantly better with aliskiren compared with

TABLE 1. Patient demographic and disease characteristics at randomization (randomized set)

	Aliskiren ($n = 414$)	Telmisartan ($n = 408$)
Age (years)	55.8 ± 11.46	56.0 ± 11.91
≥65 years, *n* (%)	96 (23.2)	102 (25.0)
Sex, *n* (%)		
Male	208 (50.2)	230 (56.4)
Female	206 (49.8)	178 (43.6)
Race, *n* (%)		
White	227 (54.8)	225 (55.1)
Black	6 (1.4)	1 (0.2)
Asian	98 (23.7)	98 (24.0)
Native American	0	1 (0.2)
Other	83 (20.0)	83 (20.3)
BMI (kg/m^2)	28.93 ± 5.192[a]	29.15 ± 5.127[b]
Obese, *n* (%)	140 (33.8)[a]	154 (37.7)[b]
Duration of hypertension (years)	7.8 ± 7.13[c]	6.9 ± 6.81[d]
Diabetes, *n* (%)	47 (11.4)	55 (13.5)
24-h MASBP (mmHg)	146.1 ± 9.22[e]	146.9 ± 9.54[f]
24-h MADBP (mmHg)	88.2 ± 9.29[e]	88.3 ± 9.51[f]
msSBP (mmHg)	155.4 ± 10.10[g]	155.9 ± 10.16[h]
msDBP (mmHg)	90.1 ± 9.77[g]	90.4 ± 9.19[h]

Data are presented as mean ± SD, unless otherwise stated. Obese was defined as BMI ≥30 kg/m^2. Diabetes was defined as having a prior history of diabetes mellitus or having used oral antidiabetics or insulin at any time on or prior to study entry. Ambulatory blood pressure monitoring visits spanned 2 days (starting on day −1 and ending on day 1). MADBP, mean ambulatory DBP; MASBP, mean ambulatory SBP; msDBP, mean sitting DBP; msSBP, mean sitting SBP.
[a] $n = 409$.
[b] $n = 404$.
[c] $n = 382$.
[d] $n = 386$.
[e] $n = 407$.
[f] $n = 403$.
[g] $n = 413$.
[h] $n = 408$.

TABLE 2. Change in ambulatory blood pressure monitoring and office blood pressure from end of 12 weeks of active treatment to end of 7-day treatment withdrawal

			Pair-wise comparison (aliskiren vs. telmisartan)		
Overall population	**Aliskiren**	**Telmisartan**	**LSM difference in change from baseline ± SEM**	**95% CI for LSM difference**	***P* value**
ABPM (ABPM completer set)	$N=344$	$N=346$			
24-h MASBP (mmHg)	$n=330$	$n=336$			
Mean at EoA (week 12)	134.30	134.26			
Change from EoA at EoW, LSM ± SEM[a]	2.70 ± 0.466	6.51 ± 0.461	−3.81 ± 0.632	−5.05, −2.57	<0.0001[b]
24-h MADBP (mmHg)	$n=330$	$n=336$			
Mean at EoA (week 12)	80.95	80.47			
Change from EoA at EoW, LSM ± SEM[a]	2.09 ± 0.328	4.21 ± 0.324	−2.12 ± 0.444	−2.99, −1.24	<0.0001[b]
Office BP (full analysis set)	$N=412$	$N=406$			
msSBP (mmHg)	$n=369$	$n=363$			
Mean at EoA (week 12)	140.07	140.74			
Change from EoA at EoW, LSM ± SEM[a]	1.26 ± 0.652	5.00 ± 0.658	−3.74 ± 0.892	−5.49, −1.99	<0.0001[b]
msDBP (mmHg)	$n=369$	$n=363$			
Mean at EoA (week 12)	83.82	83.60			
Change from EoA at EoW, LSM ± SEM[a]	0.03 ± 0.388	2.69 ± 0.392	−2.66 ± 0.531	−3.70, −1.62	<0.0001[b]
Diabetic patient subgroup					
ABPM	$N=47$	$N=55$			
24-h MASBP (mmHg)	$n=35$	$n=45$			
Change from EoA at EoW, LSM ± SEM[a]	2.57 ± 1.753	5.83 ± 1.366	−3.26 ± 2.070	−7.39, 0.86	0.1192
24-h MADBP (mmHg)	$n=35$	$n=45$			
Change from EoA at EoW, LSM ± SEM [a]	2.30 ± 0.965	3.49 ± 0.751	−1.19 ± 1.139	−3.46, 1.08	0.2984
Office BP	$N=47$	$N=55$			
msSBP (mmHg)	$n=38$	$n=49$			
Change from EoA at EoW, LSM ± SEM [a]	6.25 ± 2.320	5.59 ± 1.813	0.66 ± 2.705	−4.73, 6.04	0.8086
msDBP (mmHg)	$n=38$	$n=49$			
Change from EoA at EoW, LSM ± SEM [a]	2.66 ± 1.188	2.23 ± 0.928	0.43 ± 1.385	−2.32, 3.19	0.7551

Pairwise comparison of aliskiren vs. telmisartan. A negative treatment difference represents a smaller increase in BP for the aliskiren group than for the telmisartan group. ABPM, ambulatory blood pressure monitoring; CI, confidence interval; EoA, end of active treatment period; EoW, end of treatment withdrawal period; LSM, least squares mean; MADBP, mean ambulatory DBP; MASBP, mean ambulatory SBP; msDBP, mean sitting DBP; msSBP, mean sitting SBP.
[a]Least squares means and the associated SEM, CI and *P* values calculated from a two-way analysis of variance model with treatment and region as factors.
[b]Indicated statistical significance at 0.05 level.

telmisartan treatment, the LSM between-treatment difference (±SEM) being −1.6 ± 0.513 mmHg ($P < 0.05$).

Change in daytime and night-time mean ambulatory SBP/mean ambulatory DBP

The increase in daytime MASBP/MADBP from EoA to EoW was greater in the telmisartan group (6.7/4.2 mmHg) than in the aliskiren group (2.6/2.0 mmHg) (Table 3), the LSM difference between treatments being significantly (both $P < 0.0001$) in favour of aliskiren.

Daytime MASBP/MADBP reduction from RAN to EoA was similar to the mean 24-h MASBP/MADBP reduction during this period and was comparable between the two treatments (Table 3). However, considering the treatment withdrawal period, the reduction in daytime MASBP/MADBP from RAN to EoW was significantly better with aliskiren (−8.6/−5.2 mmHg) compared with telmisartan (−5.6/−3.5 mmHg); the LSM difference between treatments being −3.0/−1.7 mmHg (both $P < 0.01$).

Similar results were seen for change in night-time MASBP/MADBP from EoA to EoW and from RAN to EoW (Table 3).

Change in last 4-h mean ambulatory SBP and mean ambulatory DBP (morning surge)

Mean values for hourly MASBP and MADBP showed typical diurnal fluctuations with peak decreases in BP at approximately 4-h postdose for both aliskiren and telmisartan, as expected (Fig. 3).

BP changes in the last 4 h of the dosing period represent the morning surge in BP. After the 7-day treatment withdrawal period, mean SBP and DBP in this critical 4-h period increased less significantly from EoA to EoW in the aliskiren compared with the telmisartan group (Table 3; 1.7/1.6 and 5.2/3.3 mmHg, respectively; the LSM between-treatment difference being −3.47/−1.73 mmHg, $P < 0.01$). The last 4-h MASBP/MADBP was comparable for both treatment groups from RAN to EoA, but was significantly lower with aliskiren at EoW ($P < 0.05$) (Table 3).

Change in office SBP/DBP

The results for office BP were consistent with the results obtained with standard ABP measurements. During the 7-day treatment withdrawal, msSBP/msDBP increased less significantly in the aliskiren group than in the telmisartan group (Table 2). The between-treatment LSM difference was statistically significant and in favour of aliskiren (−3.74/−2.66 mmHg; both $P < 0.0001$).

Clinically comparable LSM reduction in msSBP/msDBP from RAN to EoA was observed with aliskiren (−15.1/−6.3 mmHg) and telmisartan (−14.7/−6.6 mmHg) treatment (Fig. 4). Office BP was also assessed on day 2 of the treatment withdrawal period after one omitted dose. msSBP (±SEM) from EoA to day 2 of the treatment

TABLE 3. Ambulatory blood pressure monitoring and office blood pressure-related parameters (summary statistics and full analysis set)

Parameter	Treatment group	RAN	EoA	Day 2	EoW	RAN to EoA	RAN to EoW	EoA to day 2	EoA to EoW
Ambulatory blood pressure measurements, mean ± SD (mmHg)									
MASBP									
24-h	Aliskiren	146.1 ± 9.23	134.7 ± 11.22	–	137.0 ± 10.45	−11.2 ± 11.06	−8.4 ± 10.40	–	2.5 ± 8.04
	Telmisartan	146.9 ± 9.52	134.6 ± 12.72	–	140.7 ± 11.59	−12.5 ± 10.83	−6.2 ± 9.86	–	6.3 ± 8.24
Daytime	Aliskiren	149.0 ± 9.48	137.4 ± 11.61	–	139.8 ± 10.66	−11.3 ± 11.69	−8.6 ± 10.92	–	2.6 ± 8.64
	Telmisartan	149.8 ± 9.61	137.0 ± 13.02	–	143.6 ± 11.92	−12.9 ± 11.34	−6.2 ± 10.08	–	6.7 ± 8.49
Night-time	Aliskiren	135.1 ± 12.18	124.5 ± 12.66	–	126.0 ± 12.50	−10.4 ± 11.63	−8.1 ± 11.61	–	2.0 ± 9.28
	Telmisartan	136.3 ± 12.67	125.2 ± 13.57	–	129.8 ± 13.50	−11.1 ± 12.15	−6.5 ± 12.60	–	4.6 ± 10.82
Last 4-h	Aliskiren	144.9 ± 12.20	133.7 ± 14.18	–	134.4 ± 13.14	−10.8 ± 13.31	−9.4 ± 12.83	–	1.7 ± 11.50
	Telmisartan	145.7 ± 12.37	134.0 ± 14.39	–	139.2 ± 14.40	−11.9 ± 12.43	−6.5 ± 12.23	–	5.2 ± 11.43
MADBP									
24-h	Aliskiren	88.3 ± 9.30	81.1 ± 9.29	–	82.9 ± 9.42	−7.2 ± 7.23	−5.2 ± 7.12	–	2.0 ± 5.49
	Telmisartan	88.3 ± 9.53	80.7 ± 9.54	–	84.7 ± 9.82	−7.8 ± 7.23	−3.7 ± 7.02	–	4.1 ± 5.94
Daytime	Aliskiren	90.8 ± 9.53	83.5 ± 9.51	–	85.3 ± 9.78	−7.4 ± 7.48	−5.4 ± 7.56	–	2.0 ± 5.91
	Telmisartan	90.7 ± 9.75	82.9 ± 9.78	–	87.1 ± 9.95	−8.0 ± 7.65	−3.8 ± 7.22	–	4.2 ± 6.28
Night-time	Aliskiren	79.2 ± 10.27	72.4 ± 9.87	–	74.0 ± 9.40	−6.8 ± 8.29	−5.0 ± 7.83	–	1.9 ± 6.38
	Telmisartan	79.6 ± 10.27	72.8 ± 9.89	–	76.2 ± 11.06	−7.0 ± 8.20	−3.8 ± 8.76	–	3.2 ± 7.59
Last 4-h	Aliskiren	88.2 ± 10.53	80.8 ± 11.00	–	81.7 ± 10.74	−7.5 ± 9.04	−6.3 ± 9.23	–	1.6 ± 8.52
	Telmisartan	88.4 ± 10.50	80.8 ± 10.80	–	84.1 ± 11.27	−8.1 ± 8.94	−4.5 ± 8.64	–	3.3 ± 7.91
Office blood pressure measurements, mean ± SD (mmHg)									
msSBP	Aliskiren	155.4 ± 10.10	140.3 ± 14.45	139.4 ± 14.49	141.4 ± 14.48	−15.2 ± 14.51	−14.0 ± 14.13	−0.8 ± 12.22	1.2 ± 12.15
	Telmisartan	155.9 ± 10.16	141.0 ± 15.98	141.6 ± 14.71	145.9 ± 13.73	−15.0 ± 14.67	−10.0 ± 13.41	1.2 ± 12.32	5.0 ± 11.97
msDBP	Aliskiren	90.1 ± 9.77	83.7 ± 10.50	82.4 ± 10.66	84.0 ± 9.91	−6.4 ± 9.25	−6.3 ± 8.78	−1.2 ± 7.79	0.2 ± 7.13
	Telmisartan	90.4 ± 9.20	83.8 ± 10.18	83.4 ± 9.98	86.3 ± 9.93	−6.9 ± 9.11	−4.1 ± 8.35	−0.1 ± 7.54	2.8 ± 7.24

EoA, end of active treatment period (week 12); EoW, end of 7-day treatment withdrawal period (week 13); last 4-h, mean blood pressure changes in the last 4 h of the dosing period; MADBP, mean ambulatory DBP; MASBP, mean ambulatory SBP; msDBP, mean sitting DBP; msSBP, mean sitting SBP; RAN, randomization.

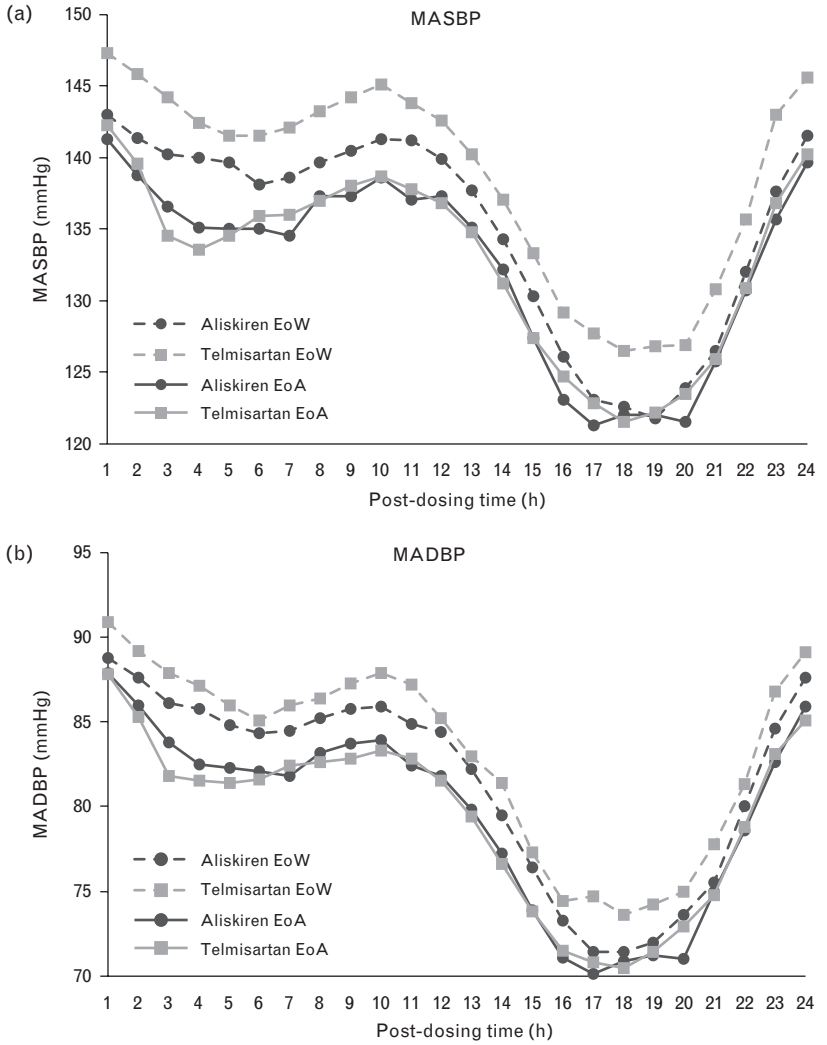

FIGURE 3 Mean hourly ambulatory blood pressure at end of active treatment and end of withdrawal (full analysis set). EoA, end of active treatment; EoW, end of withdrawal; MASBP, mean ambulatory systolic blood pressure; MADBP, mean ambulatory diastolic blood pressure.

withdrawal period decreased by -0.7 ± 0.672 mmHg in the aliskiren group and increased by 1.3 ± 0.670 mmHg in the telmisartan group, the between-treatment difference being significantly (2.0 mmHg, $P = 0.0295$) in favour of aliskiren treatment (Fig. 4). Consequently, the overall msSBP reduction from RAN to day 2 of treatment withdrawal period was significantly ($P = 0.0249$) better with aliskiren (-16.0 ± 0.726 mmHg) compared with telmisartan (-13.8 ± 0.723 mmHg), the between-treatment difference being -2.2 ± 0.991 mmHg in favour of aliskiren. In addition, msDBP decreased between EoA and day 2 of the treatment withdrawal in both treatment groups, with a more pronounced decrease in the aliskiren group (-1.3 ± 0.418 mmHg) vs. the telmisartan group (-0.2 ± 0.417 mmHg, LSM between-treatment difference: -1.1 mmHg, $P = 0.0569$).

When considering the extended treatment period including treatment withdrawal, the overall reduction in msSBP/msDBP from RAN to EoW was significantly higher for aliskiren as compared with telmisartan treatment, the LSM between-treatment difference being $-4.2/-2.3$ mmHg, and in favour of aliskiren treatment (both, $P < 0.0001$).

BIOMARKERS

Aldosterone, PRA and PRC levels at RAN, EoA and EoW for the subset of patients who underwent biomarker assessments ($n = 335$) are shown in Fig. 5. The percentage change is expressed as Geo-mean change. After 12 weeks of active treatment, plasma aldosterone levels decreased by 24.3% with aliskiren (184.6 pmol/l at RAN to 139.2 pmol/l at EoA) and by 19.6% with telmisartan (167.1 pmol/l at RAN to 139.8 pmol/l at EoA). After 7-day treatment withdrawal (EoW), aldosterone levels remained significantly below those observed at baseline in the aliskiren group (-19.9% EoA compared with RAN baseline, $P < 0.0121$ vs. telmisartan), whereas in the telmisartan group, plasma aldosterone levels returned to near baseline levels (167.2 pmol/l at RAN; 169.5 pmol/l at EoW; Supplemental Table 1, http://links.lww.com/HJH/A161). After 12 weeks of active treatment, aliskiren reduced PRA by 78.9% from

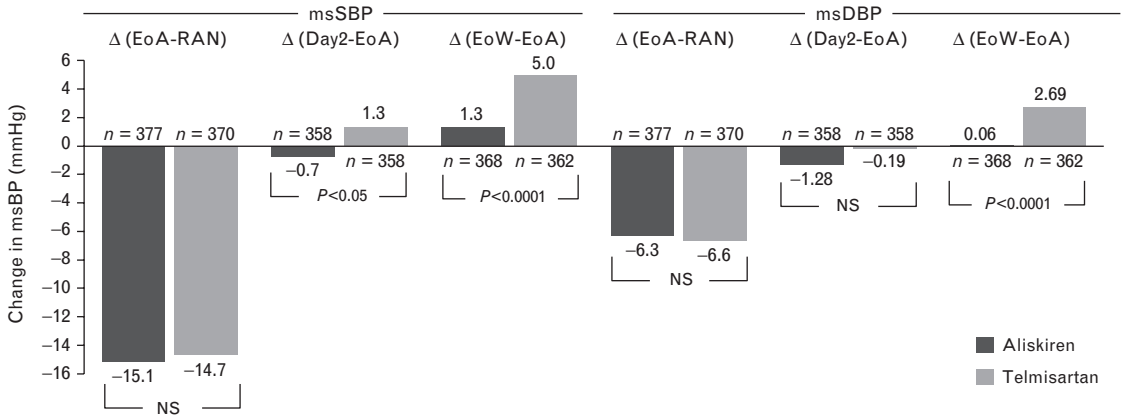

FIGURE 4 Change in mean sitting systolic and diastolic blood pressure at the end of active treatment and during the treatment withdrawal period (full analysis set). EoA, end of active treatment; EoW, end of withdrawal; msSBP, mean sitting systolic blood pressure; msDBP, mean sitting diastolic blood pressure; NS, not significant; RAN, randomization.

RAN to EoA (0.752 ng/ml per h at RAN to 0.170 ng/ml per h at EoA) with the reduction maintained after 7-day treatment withdrawal (0.224 ng/ml per h at EoW). In the telmisartan group, PRA increased by 232.2% after 12 weeks of active treatment (0.589 ng/ml per h at RAN to 2.080 ng/ml per h at EoA) and returned toward RAN levels after 7-day treatment withdrawal (0.819 ng/ml per h at EoW, Supplemental Table 1, http://links.lww.com/HJH/A161). After 12 weeks of active treatment, both aliskiren and telmisartan increased PRC, with greater increases observed with aliskiren (6.950 ng/l at RAN to 37.743 ng/l at EoA with aliskiren; 5.875 ng/l at RAN to 18.053 ng/l with telmisartan). After 7-day treatment withdrawal, PRC decreased compared with EoA levels in both treatment groups; however, the decrease was more pronounced with telmisartan compared with aliskiren (Supplemental Table 1, http://links.lww.com/HJH/A161).

EFFICACY IN THE SUBGROUP OF PATIENTS WITH DIABETES

An increase in 24-h MASBP and MADBP from EoA to EoW was observed with both treatments, the LSM change (±SEM) being numerically higher in telmisartan than in the aliskiren treatment group (nonsignificant; Table 2). Clinically comparable LSM reductions in msSBP/msDBP from RAN to EoA were observed with aliskiren (−11.6/−4.5 mmHg) and telmisartan (−12.4/−3.3 mmHg) treatment (Supplemental Tables 2 and 3, http://links.lww.com/HJH/A161). During the 7-day treatment withdrawal, msSBP increased to a lesser extent in the aliskiren group than in the telmisartan group (Table 2).

SAFETY AND TOLERABILITY

Both aliskiren and telmisartan were well tolerated. A similar proportion of patients in both treatment groups reported one or more adverse events during the 12 weeks of active treatment or 7-day treatment withdrawal (Table 4): 148 (36.0%) patients in the aliskiren group compared with 164 (40.7%) in the telmisartan group. The most frequently reported adverse events were headache (3.6% in the aliskiren vs. 7.9% in the telmisartan group) and nasopharyngitis (3.6% in the aliskiren vs. 4.7% in the telmisartan group). During the withdrawal period alone there were few adverse events. The incidence of adverse events within the subgroup of patients with diabetes was consistent with the overall population.

There were two deaths: a 38-year-old woman died of a brain haemorrhage during the placebo run-in period, prior to RAN; and, a 72-year-old man died of acute myocardial infarction during treatment with telmisartan. Both deaths were attributed to progression of underlying disease by the investigators.

A total of eight patients experienced SAEs after RAN: three (0.7%) in the aliskiren and five (1.2%) in the telmisartan group. SAEs in the aliskiren group were acute myocardial infarction, acute pancreatitis and transient ischaemic attack. SAEs in the telmisartan group were acute myocardial infarction, unstable angina, diverticulitis, femoral fracture and ischaemic stroke. None of the SAEs were considered to be related to the study medications. There were no SAEs reported in either treatment group during the 7-day treatment withdrawal period. There were few patients with adverse events leading to discontinuation in both treatment groups, with most events being related to control of BP.

Notably, abnormal values for potassium, blood urea nitrogen and creatinine concentrations were observed with a similarly low incidence in both treatment groups (Table 4). Over the course of the study, no clinically meaningful differences between treatment groups were observed with respect to haematology or biochemistry parameters or vital signs.

DISCUSSION

This study (ASSERTIVE) demonstrates that loss of antihypertensive treatment efficacy over a 7-day period of simulated nonadherence is significantly slower with aliskiren compared with telmisartan. Differences in BP-lowering efficacy and the advantage of aliskiren were already evident after a single missed dose and increased over the 7-day treatment withdrawal period.

English dictionaries define the term 'forgiveness' as 'to grant free pardon and to give up all claim on account of an

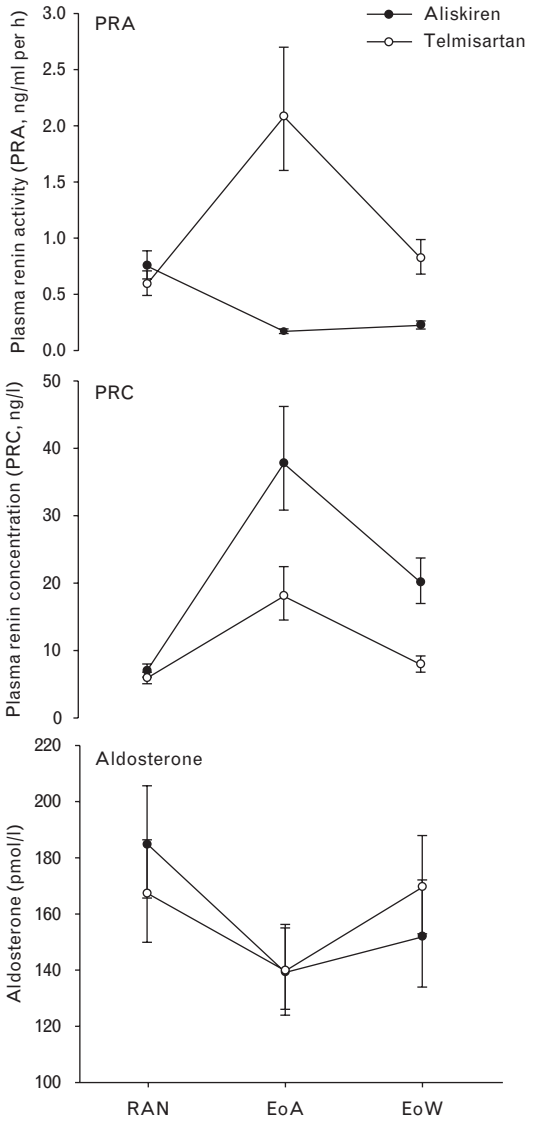

FIGURE 5 Biomarker measurements, plasma renin activity, plasma renin concentration, and plasma aldosterone, by treatment group (biomarkers completer set). Results expressed as geometric means and their 95% CI at each time point. CI, confidence interval; EoA, end of active treatment; EoW, end of withdrawal; RAN, randomization.

offence or debt.' This term has also been applied to drugs that, due to their sustained efficacy, provide protection to patients who are nonadherent to treatment. Therefore, drugs with sustained BP-lowering efficacy are deemed to provide a high degree of forgiveness in which efficient BP control may be achieved despite irregular intake of medications. In fact, the degree of forgiveness of a given drug may be a powerful predictor of cardiovascular protective efficacy of the drug [12]. Amlodipine and atenolol represent examples of drugs that demonstrate a correlation between the degree of forgiveness and cardiovascular risk reduction. Amlodipine is a long-acting dihydropyridine calcium channel blocker that has shown excellent results in several hypertension intervention trials such as the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial [26], or the Valsartan Antihypertensive Long-term Use Evaluation Trial [27]. In contrast, the short-acting ß-blocker atenolol [9] provided disappointing results in many hypertension intervention studies [28,29], despite similar BP reduction efficacy of the two drugs. It is noteworthy that these results were obtained in randomized controlled trials in which adherence to medication is substantially greater than in clinical practice [30]. The advantage of drugs that safely forgive one or more days of interruption of dosing may, thus, be even greater in clinical practice than that shown in controlled trials.

The direct renin inhibitor aliskiren and the ARB telmisartan block the RAAS cascade at different points and are the longest acting drugs from their respective classes. Both aliskiren and telmisartan have demonstrated effective BP-lowering efficacy in previous studies [26–28].

This study evaluated the changes in ABP as well as office BP with results that were similar for both measurements and in favour of aliskiren treatment. Office BP measurements were also used to evaluate the relative antihypertensive efficacy after a single missed dose. It was observed that both aliskiren and telmisartan are sufficiently long acting to sustain BP lowering through the 24-h period after drug intake, including the critical early morning period. However, after a single dose omission, the antihypertensive effect was tentatively lost with telmisartan, evidenced by a 1.3 mmHg increase in msSBP, whereas with aliskiren msSBP decreased further by 0.7 mmHg despite the omitted dose. The difference between these treatments was statistically significant and clinically relevant, especially in light of the fact that approximately 40% of all dose omissions are for a single day. Further, as a result of this sustained efficacy of aliskiren after the missed dose, the overall msSBP reduction from the time of RAN to day 2 of the treatment withdrawal period was significantly better with aliskiren compared with telmisartan.

Highly significant differences in BP reduction were also observed after repeated dose omissions at the end of the 7-day withdrawal period. It was observed that 51% of the 24-h SBP lowering achieved following 12 weeks of treatment with telmisartan was lost at the end of the 7-day treatment withdrawal period, whereas the respective loss in BP control was only 22% in aliskiren-treated patients (Table 3). These results should be appreciated on the basis of the fact that almost 60% of all missed doses are part of a larger sequence of missed doses for 2 or more days.

Once-daily antihypertensive drugs are typically taken in the morning, and generally show their peak antihypertensive effect within 2–4 h. Trough effects occur the next morning before the next dose is taken. Due to regulations associated with waking, patients experience a morning surge in BP during the last 4–6 h before dosing when the BP-lowering activity is at its lowest. Although the two drugs achieved similarly low BP during the active treatment period, after a 7-day missed dose period aliskiren demonstrated significantly reduced BP, lower BP variation and smoother, better sustained 24-h therapeutic coverage than telmisartan. These results are in line with results from previous studies with aliskiren in which sustained BP-lowering efficacy was observed after treatment withdrawal [20,21]. In the subgroup of patients with diabetes, aliskiren showed a similar trend in BP reductions to the overall population. Aliskiren treatment also showed that after a

TABLE 4. Safety and tolerability of aliskiren and telmisartan (safety set)

	Aliskiren ($N = 411$)	Telmisartan ($N = 403$)
During treatment withdrawal period only		
Any AE	33 (8.0)	41 (10.2)
Deaths	0	0
SAEs	0	0
After randomization (12 weeks of active treatment with 7-day treatment withdrawal)		
Any AE	148 (36.0)	164 (40.7)
Deaths[a]	0	1 (0.2)
SAEs	3 (0.7)	5 (1.2)
Discontinuations due to AE	9 (2.2)	14 (3.5)
Most frequent AEs (≥3% in any group)		
Headache	15 (3.6)	32 (7.9)
Nasopharyngitis	15 (3.6)	19 (4.7)
Laboratory abnormalities	$n = 404$	$n = 397$
Serum potassium		
<3.5 mmol/l	9 (2.2)	3 (0.8)
>5.5 mmol/l	7 (1.7)	5 (1.3)
≥6.0 mmol/l	5 (1.2)	2 (0.5)
Blood urea nitrogen		
>14.28 mmol/l	0	0
Creatinine		
>176.8 μmol/l	1 (0.2)	0

Data are shown as number (percentage) of patients. AE, adverse event; SAE, serious adverse event.
[a]An additional patient died (brain herniation) during the placebo run-in period (prior to randomization) (see Fig. 2).

week of treatment interruption, the BP increase was numerically smaller compared with telmisartan. Aliskiren treatment provides more sustained BP efficacy in the general hypertensive population, as well as in high-risk patients with diabetes, and, therefore, may provide additional cardiovascular protection than telmisartan in patients in whom the regimen is not consistently followed. The impact of nonadherence on cardiovascular mortality remains to be confirmed with further prospective outcome studies.

The observed BP findings during the treatment withdrawal period may be explained, at least in part, by the results obtained on biomarkers in the present study. Thus, the sustained BP-lowering effect for aliskiren correlated with a persistent suppression of PRA on day 7 of the withdrawal period. Aldosterone levels also remained subbaseline at this time in the aliskiren group. It appears legitimate, therefore, to postulate persistent RAAS suppression as the main mechanism by which aliskiren exhibits its sustained BP-lowering effect. In contrast, PRA activity returned to the baseline range after a 7-day interruption of telmisartan administration. This suggests that the positive feedback on PRA, and therefore telmisartan blockade of angiotensin II receptors has waned at that time.

In conclusion, aliskiren provides sustained lowering of BP over and beyond a 24-h dosing period. Aliskiren, due to its unique mode of action, is capable of ensuring more efficient BP control than telmisartan despite a 7-day sequence of missed doses. Antihypertensive agents with a sustained duration of action may provide therapeutic coverage during 1 day and longer interruption of therapy. Forgiving drugs, such as aliskiren, may, thus, help to mitigate the dangers of poor patient adherence.

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Conflicts of interest

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R.D. has received research support from Novartis and has acted as a consultant for Novartis. P.B., IY.B. and F.B. have been involved in the design, conduct, analysis and reporting of the study; they are employees of Novartis (Novartis Pharma AG, Basel, Switzerland) and are, therefore, eligible for Novartis stock and stock options.

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