Sustained Blood Pressure–Lowering Effect of Aliskiren Compared With Telmisartan After a Single Missed Dose

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PATIENTS AND METHODS

Study Design

ASSERTEVE was a randomized, double-blind, double-dummy, parallel-group, multicenter study conducted...
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to compare the BP-lowering efficacy of aliskiren with telmisartan using 24-hour ambulatory BP measurement. The study design and main results have been published elsewhere.\(^\text{16}\)

Following a washout and placebo run-in period of 2 to 4 weeks, patients entered a 12-week active-treatment period and were randomized to receive either once-daily aliskiren or telmisartan. For the initial 2 weeks after randomization, patients received aliskiren 150 mg or telmisartan 40 mg and were then force-titrated to double the initial dose for 10 weeks to the EOA. Subsequently, both treatments were withdrawn for 1 week and all patients received placebo during this period.\(^\text{16}\) BP changes from EOA to EOW represented the primary endpoint. The focus of this prespecified analysis was the efficacy of aliskiren compared with telmisartan after a single missed dose, ie, day 2.

Patients
Men or women 18 years and older with a diagnosis of stage 1 and 2 hypertension with the double-entry criteria of mean sitting systolic blood pressure (msSBP) \( \geq 140 \) mm Hg and \(< 180 \) mm Hg and 24-hour mean ambulatory systolic blood pressure (maSBP) \( \geq 135 \) mm Hg at randomization were included in the study. Detailed inclusion and exclusion criteria have been published previously.\(^\text{16}\)

The trial was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation guidelines, and to higher standards in clinical research and the trial protocol was approved by independent ethics committees at all centers. The trial is registered as EudraCT no. 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.

Efficacy Assessments
In order to assess treatment effects on BP, both msSBP (msSBP) and mean sitting diastolic blood pressure [msDBP]) and (maDBP) methodologies were used. The primary efficacy assessment for this prespecified analysis was the change in BP from EOA to day 2. Change from randomization to EOA was also assessed. The msSBP was measured using an automated and validated BP-measuring device (Omron HEM-705, Bannockburn, IL) with the appropriate cuff size provided to all investigative sites and was calculated from 3 measurements taken at 1- to 2-minute intervals after the patient had been sitting for 5 minutes.

ABPM over 24 hours at randomization, EOA, and day 2 was assessed using a wrist device, BPro N6002C (HealthSTATS International, Hoe Huat Industrial Building, Singapore) on the dominant arm. ABPM over 24 hours was automatically recorded at 15-minute intervals (96 BP values). The BPro device measures BP using a hemispherical sensor plunger that impinges on the radial artery over the radius bone. The system transfers pressure forces to the internal pressure sensor. The procedure requires calibration against the standard cuff measurement and baseline setup. Baseline values were obtained prior to the start of study drug administration. Intermediate recordings were performed for a continuous duration of 10 to 60 seconds every 15 minutes. Data were stored in a computer connected to the device, equipped with the appropriate software, and an electronic copy of the recording was sent to a centralized laboratory (Core Lab Partners, Washington, DC).

Safety Analyses
Safety assessments were performed throughout the study and included recording all reported adverse events (AEs) and serious adverse events (SAEs). Laboratory tests (hematology and blood chemistry) were regularly monitored and vital signs were regularly assessed.

Statistical Analyses
The full analysis set (FAS) included all randomized patients following the intent-to-treat (ITT) principle, excluding those who had been randomized incorrectly and without study medication. The BPro ABPM completer set included all patients in the FAS who had BPro 24-hour ABPM measurements at randomization, EOA, and day 2 following the ITT principle. Patients were analyzed according to the treatment group they were assigned to at randomization. All statistical analyses were performed using SAS software version 9.1 or higher (SAS Institute, Inc, Cary, NC).

The power calculation was performed to satisfy the assumptions of the main ASSERTIVE trial, and no formal testing was foreseen for the current subanalysis. A sample size of 592 patients completing the study (296 patients per treatment group) was determined to have 80% power for the superiority test at a two-sided significance level of .05. The main study assumptions were a between-treatment difference of 3 mm Hg in msSBP from EOA to EOW and a standard deviation of 13 mm Hg.

The between-treatment group differences for changes in msSBP from EOA to day 2 were analyzed using analysis of variance with treatment and region as factors. A comparison of treatment groups was performed using analysis of covariance for changes in msSBP from randomization to EOA and in 24-hour ABPM from EOA to day 2 and randomization to EOA, with baseline as covariate and treatment and region as factors. For the changes in ABPM from EOA to day 2, data from the BPro ABPM completer set were assessed, whereas the remainder of the efficacy assessments used the FAS. Standard descriptive analyses were used to analyze safety parameters.
RESULTS

Patient Disposition and Baseline Characteristics

In the main ASSERTIVE trial, of 1359 patients who entered the placebo run-in period, 822 were randomized and 722 patients completed the study.16 In this substudy, data for the 24-hour ABPM from the BPro device were available for a total of 305 patients (37.1% of the overall study patients; BPro ABPM completer set): 158 patients assigned to aliskiren and 147 patients assigned to telmisartan completed the study.

For the total randomized population and the BPro ABPM completer set, the demographic and baseline characteristics such as diabetes status, baseline BP, and concomitant medication of both the aliskiren and telmisartan groups were comparable. Dietary influences such as salt intake were not considered to be imbalanced due to the size and global nature of the trial. In both treatment arms, the majority of patients included were Caucasian, about one third of the population was obese (body mass index ≥30 kg/m²), and the mean duration of hypertension was 7.4 years. msSBP at randomization was similar for both treatment groups.16

Efficacy

For the aliskiren and telmisartan groups, baseline values (randomization) for msSBP/msDBP were 155.4/90.1 mm Hg and 155.9/90.4 mm Hg, respectively, and for 24-hour msSBP/msDBP were 142.2/86.8 mm Hg and 145.9/88.9 mm Hg, respectively. At EOA, the msBP (assessed by the Omron device) and 24-hour ABPM (assessed by the BPro device) were similar between the treatment groups, which allowed the possibility to assume that the values at EOA could be used as the new baseline in order to evaluate the withdrawal period. The msSBP/msDBP was 140.3/83.7 mm Hg and 141.0/83.8 mm Hg and 24-hour msSBP/msDBP was 135.2/83.5 mm Hg and 135.5/84.2 mm Hg at EOA in the aliskiren and telmisartan groups, respectively.

From EOA to day 2, aliskiren maintained the reduction in msSBP (−0.7 mm Hg), whereas telmisartan treatment resulted in an increased msSBP (1.3 mm Hg). The least-squares mean (LSM) change between-treatment difference from EOA to day 2 (−2.0 mm Hg) was statistically significant in favor of aliskiren (P<.0295) (Figure 1a,b). The reductions in msDBP were numerically (not statistically significant) greater in the aliskiren group (−1.3 mm Hg) compared with the telmisartan group (−0.2 mm Hg), with a between-treatment difference of −1.1 mm Hg (P<.0569). Similar reductions were observed in both treatment groups during the active treatment period for both msSBP and msDBP (Figure 2a,b).

A sustained decrease in 24-hour msSBP from EOA to day 2 in the aliskiren group was observed, which was greater than that in the telmisartan group, with an LSM change between-treatment difference of −6.13 mm Hg (P<.0032). Telmisartan provided a numerically greater reduction (not statistically significant) than aliskiren during active treatment from randomization to EOA (Figure 3). Similarly, 24-hour msDBP was decreased in the aliskiren group after the omission of a single dose from EOA to day 2, whereas there was an increase in the telmisartan group, with the LSM change between-treatment difference (−4.10 mm Hg) significantly in favor of aliskiren (P=.0042), despite similar reductions in both treatment groups from randomization to EOA (Figure 4).

Safety and Tolerability

The proportion of patients reporting ≥1 AEs during the whole study duration was 148 (36.0%) in the aliskiren group and 164 (40.7%) in the telmisartan group. Headache and nasopharyngitis were the most common AEs reported in both treatment groups.

Aliskiren and telmisartan were both well tolerated. Detailed safety and tolerability findings from the study have been published elsewhere.16

![FIGURE 1. Least-squares mean (LSM) change in msSBP at the time points of interest (a) and mean sitting systolic blood pressure (msSBP) over time (b) (full analysis set). *P<.05 (aliskiren vs telmisartan); §baseline. Day 2 indicates day 2 after the end of active treatment; EOA, end of active treatment; RAN, randomization; SE, standard error.](image-url)
DISCUSSION

The results of this substudy of the ASSERTIVE trial show that both aliskiren and telmisartan are effective treatment options for lowering mean sitting and ambulatory BP over 24 hours. However, after a simulated single missed dose, aliskiren had a more sustained effect on BP compared with telmisartan, which lost some of its anti-hypertensive efficacy in this patient population.

In a large proportion of treated patients with hypertension, BP remains uncontrolled despite the wide availability of antihypertensive agents that have proven clinical efficacy in controlled trials. Poor adherence with the prescribed medication, including missed doses for variable lengths of time, is common especially in patients with hypertension because of the asymptomatic nature of the disease. In clinical trials using electronic medication monitoring, approximately 10% of patients miss a scheduled dose of their antihypertensive medication on any given day. In real-world clinical practice, the proportion of patients with dose omission has been shown to markedly exceed the numbers observed in controlled trials. As a consequence, treatment benefit may be lower in a real-world setting compared with clinical trials, possibly mediated by the intermittent loss of BP-lowering efficacy with irregular intake of the prescribed medication.

FIGURE 2. Least-squares mean (LSM) change in mean sitting diastolic blood pressure (msDBP) at the time points of interest (a) and msDBP over time (b) (full analysis set). Baseline. Day 2 indicates day 2 after the end of active treatment; EOA, end of active treatment; RAN, randomization; SE, standard error.

FIGURE 3. Least-squares mean (LSM) change in 24-hour mean ambulatory systolic blood pressure (maSBP) (full analysis set for randomization [RAN] to the end of active treatment [EOA] for data from the SpaceLabs device and the BPro ABPM completer set RAN to EOA, RAN to day 2, and EOA to day 2 for data from the BPro device). *P < .05, **P < .01 (aliskiren vs telmisartan); baseline. Day 2 indicates day 2 after the end of active treatment; SE, standard error.

FIGURE 4. Least-squares mean (LSM) change in 24-hour mean ambulatory diastolic blood pressure (maDBP) (full analysis set and BPro ABPM completer set). **P < .01 (aliskiren vs telmisartan); baseline. Day 2 indicates day 2 after the end of active treatment (EOA); maSBP, mean ambulatory systolic blood pressure; RAN, randomization; SE, standard error.
maintain their effects even during one or even a series of inadvertently missed doses.

Several studies have investigated whether antihypertensives offer protection against loss of BP control in patients with hypertension after a simulated missed dose (Table). Betaxolol, a β-adrenergic antagonist, which has a longer elimination half-life (14–22 hours) compared with atenolol (6–7 hours) was shown to be associated with prolonged BP-lowering efficacy during a single dose omission. Amlodipine, a long-acting calcium channel blocker, was more effective compared with enalapril during a missed dose, despite similar efficacy during active treatment. In addition, the ARB candesartan cilexetil was shown to be superior to losartan in reducing BP on the day of a missed dose.

The ARB telmisartan has been demonstrated to be superior to losartan, valsartan, amlodipine, and ramipril for sustaining the BP-lowering efficacy at the end of the 24-hour dosing interval, during the early morning hours, when the efficacy of most antihypertensive drugs decline. Moreover, in the event of a missed dose, telmisartan has shown superiority over valsartan in reducing BP.

Aliskiren, which inhibits the RAAS system at an early stage, yielded similar results. In a randomized double-blind study, aliskiren demonstrated significant (P < .01) and more sustained BP-lowering efficacy after a single missed dose compared with both the ACE inhibitor ramipril and the ARB irbesartan. Furthermore, approximately 80% of the BP-lowering effect of aliskiren was maintained even after 4 days of stopping active treatment in a randomized, double-blind, dose-finding study. Similarly, in a 6-month double-blind comparator study of aliskiren- and ramipril-based therapy, the BP-lowering effect was more prolonged after discontinuing aliskiren-based therapy compared with discontinuation of ramipril-based therapy.

The time-dependent efficacy of drugs acting on the RAAS after ≥1 missed doses can also be evaluated by measuring the effect on biomarkers such as plasma renin activity (PRA) and aldosterone. Studies have demonstrated that aliskiren significantly reduces PRA levels during treatment and that this reduction is maintained following cessation of treatment for up to 2 weeks. Aliskiren withdrawal after 8-week therapy in 672 patients with mild to moderate hypertension was not associated with BP or PRA rebound, and PRA remained suppressed even after 2 weeks of treatment discontinuation. In contrast, PRA levels are increased with ACE inhibitors and ARBs, and increased PRA may be an indicator for the duration of action after missed doses. This biomarker may therefore represent an integrated way to assess the pharmacologic level of RAAS blockade, accounting for the pharmacokinetics and biological activities of both aliskiren and telmisartan on renin and angiotensin II receptors, respectively. A similar approach has been experimentally proposed for the assessment of patients’ compliance.

The prolonged efficacy of aliskiren is also supported by data from 6 clinical trials that revealed aliskiren’s sustained BP-lowering efficacy for longer than 1 week of treatment withdrawal compared with competitors with a shorter duration of action. The efficacy of aliskiren and its long duration of action, despite the low bioavailability, are largely attributed to its high potency for inhibition of human renin and its long half-life (~40 hours) and tissue affinity. Aliskiren penetrates adipose and skeletal muscle tissue and reduces RAAS activity in patients with obesity and hypertension. Moreover, aliskiren is retained in the kidney especially in the glomeruli and renal arterioles and possibly in juxtaglomerular cells even after a 3-week washout period.

### TABLE. Summary of Studies Showing the Efficacy of Antihypertensive Agents After Missed Dose(s)

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Treatment, wk</th>
<th>Post-Dose, h</th>
<th>Mean Changes in BP, mm Hg</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td>Mean sitting blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Betaxolol (10–20 mg; n=46) vs atenolol (50–100 mg; n=50)</td>
<td>6</td>
<td>52</td>
<td>1.9/1.6 vs 7.8/3.8</td>
<td>.05/.02&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Amlodipine (5–10 mg; n=94) vs losartan (50–100 mg; n=93)</td>
<td>12</td>
<td>72</td>
<td>5.9/3.3 vs 6.0/2.6</td>
<td>NS/NS&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Amlodipine (5 mg; n=27) vs nifedipine GITS (30 mg; n=29)</td>
<td>4</td>
<td>72</td>
<td>4.9/6.7 vs 21.42/13.0</td>
<td>&lt;.001/.001&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ambulatory blood pressure monitoring</td>
<td></td>
<td></td>
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<tr>
<td>Valsartan (160 mg; n=74) vs enalapril (20 mg; n=74)</td>
<td>16</td>
<td>24–48</td>
<td>−2.1/−1.4 vs 5.5/3.8</td>
<td>.032&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Amlodipine (5–10 mg; n=97) vs nifedipine GITS (30–60 mg; n=104)</td>
<td>12</td>
<td>24–48</td>
<td>2.6/1.4 vs 5.5/3.0</td>
<td>.002/.005&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Trandolapril (2 mg; n=40) vs enalapril (20 mg; n=36)</td>
<td>3</td>
<td>24–48</td>
<td>4.4/3.6 vs 4.1/1.6</td>
<td>NA</td>
</tr>
<tr>
<td>Amlodipine (5 mg; n=24) vs enalapril (5 mg; n=25)</td>
<td>14</td>
<td>48–72</td>
<td>6.4/2.8 vs 5.6/4.1</td>
<td>NS/NS&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Amlodipine (5–10 mg; n=97) vs nifedipine GITS (30–60 mg; n=104)</td>
<td>12</td>
<td>48–72</td>
<td>4.8/2.7 vs 11.2/6.3</td>
<td>.0001/.0001&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>Amlodipine (5–10 mg; n=92) vs losartan (50–100 mg; n=91)</td>
<td>12</td>
<td>48–74</td>
<td>4.5/1.8 vs 4.3/2.4</td>
<td>NS/NS</td>
</tr>
</tbody>
</table>

Abbreviations: GITs, gastrointestinal therapeutic system; NA, not available; NS, not significant. P values are for between-treatment difference calculated using logistic regression to the difference between 52 hours post-dose to 4 hours. Analysis of variance (ANOVA) model with fixed treatment and center effects. <sup>a</sup> Student t test nonpaired. <sup>b</sup> Repeated-measures ANOVA. Least-squares means and contrast statements. <sup>c</sup> Two-sided t tests.
In this study, aliskiren has shown statistically significant BP-lowering efficacy on msSBP and 24-hour ABPM compared with telmisartan after 48 hours of treatment withdrawal. The 24-hour ABPM was measured using the BPro device, which has not been extensively used in clinical trials to date. However, the performance of the BPro device assessed with the SpaceLabs cuff device as a reference and using the data of the aliskiren group of the BPro completer set from RAN to EOA indicates that the BPro device will produce reliable measurements. Aliskiren and telmisartan were both well tolerated. Detailed safety and tolerability findings from the study have been published elsewhere.16

CONCLUSIONS

After a single missed dose, which reflects a common clinical scenario, aliskiren compared with telmisartan demonstrated a more sustained and significant BP-lowering effect on 24-hour ABPM and msBP. These results documenting the prolonged efficacy following a single missed dose support the forgiving nature of aliskiren in patients with poor medication compliance.

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References


