Antihypertensive Efficacy of the Direct Renin Inhibitor Aliskiren as Add-on Therapy in Patients with Poorly Controlled Hypertension

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Abstract

Objective A direct renin inhibitor, aliskiren, has a longer stable antihypertensive effect compared with other renin-angiotensin-aldosterone system (RAAS) inhibitors.

Methods This study was a 6-month, single-center, open trial conducted between December 2010 and November 2011 to assess the antihypertensive effect of adding aliskiren (300 mg) to the treatment of essential hypertension patients whose target blood pressure (BP) had not been achieved and to assess whether it was possible to reduce the amount of antihypertensive drugs used.

Results The results showed an overall improvement in the target BP achievement rate of 60% for clinic BP and 52% for home BP measurements (75 cases total). The mean number of drugs before treatment with aliskiren was 3.28±1.52, whereas at the end of the six months the mean number of drugs prescribed other than aliskiren was 2.85±1.72 (p<0.0001). Moreover, no worsening of the renal function was observed in patients with diabetes or chronic kidney disease (CKD) who were being treated with other RAAS inhibitors in combination to aliskiren.

Conclusion These results showed that when aliskiren was added to the treatment of poorly controlled hypertension, the BP achievement rate increased, and it was possible to reduce the amount of antihypertensive drugs used in combination with aliskiren. Moreover, as a result of careful monitoring of the renal function or decreasing the amounts of drugs used in combination, no worsening of the renal function was observed even in the cases complicated by diabetes or CKD being treated with other RAAS inhibitors.

Key words: aliskiren, hypertension, renin-aldosterone-angiotensin system


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Introduction

Strict blood pressure (BP) management is essential for preventing cardiovascular diseases, which is the purpose of antihypertensive therapy. Due to the development of exceptional antihypertensive drugs, BP management has become relatively easy in comparison with the past. Nevertheless, there have been many reports of low achievement rates (30-50%) in the BP targets recommended in the clinical practice guidelines for hypertension, and the target BP achievement rates in hypertension complicated by diabetes mellitus (DM) and chronic kidney disease (CKD) are even lower (1-4). As it stands, there are many hypertension patients whose clinical course is observed without adequate BP management.

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are used as inhibitors of the renin-angiotensin-aldosterone system (RAAS); they have been demonstrated to have excellent organ-protective effects and are in widespread use (5). It has been noted that it is difficult to adequately inhibit the RAAS system with these drugs because the factors that compose the RAAS sys-

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tion are upstream of their sites of action increase (6). How-
never, aliskiren, an RAAS system rate-limiting enzyme which
directly inhibits renin that lies furthest upstream, has been
developed in recent years. Aliskiren has been reported to
have a long half-life in the blood, i.e., 40 hours, in humans
and a longer stable antihypertensive effect than ACEIs or
ARBs (7). Aliskiren has also been reported to have an anti-
hypertensive effect that is superior to that of ACEIs and to
have an additive antihypertensive effect when used in com-
bination with ARBs, calcium antagonists, and diuretics (8).
Moreover, aliskiren has displayed an adequate antihyper-
tensive effect in double-blind trials both in Japan and abroad,
and it has been shown to have high tolerability, with no dif-
fences in the frequency of occurrence of adverse events
from placebos (9-11).

We hypothesized that aliskiren is useful for achieving a
target BP when used in combination with antihypertensive
drugs whose antihypertensive effect is insufficient. Further-
more, when the target BP is achieved by using aliskiren in
combination with antihypertensive drugs, the amounts of
other antihypertensive drugs used can be lowered.

The purpose of this study was to test our hypothesis by:
1) assessing the antihypertensive effect of aliskiren in com-
bination with other antihypertensive drugs in essential hy-
pertension patients whose target BP had not been achieved
despite receiving antihypertensive drug therapy and 2) as-
sessing the possibility of reducing the amount of antihyper-
tensive drugs used, other than aliskiren, when the target BP
had been achieved by aliskiren.

Materials and Methods

Study population and study design

This study was a single-center, single-arm, open trial to
assess the antihypertensive effect of adding aliskiren to the
treatment of essential hypertension patients who had been
taking antihypertensive drugs other than aliskiren for at least
two months without any changes in the drugs, but whose
clinic BP or home BP had not reached the target BP recom-
manded by The Japanese Society of Hypertension Guide-
lines for the Management of Hypertension (JSH2009) (12),
and, when the BP was reduced to the target BP, to assess
the possibility of reducing the amount of antihypertensive
drugs used other than aliskiren.

Because this study was concluded before the interim re-
port that many adverse events developed during the ATTI-
ITUDE trial (13), patients with diabetes and CKD or the pa-
tients taking ACEIs/ARBs are included in the study cohort.
This study was conducted between December 2010 and No-

The primary endpoints were the changes in the clinic and
home BPs during the treatment period and the target BP
achievement rate. The secondary endpoint was the amount
of change in the antihypertensive drugs prescribed other
than aliskiren.

A safety evaluation was conducted by evaluating the side
effects and their incidence (occurrence of all adverse events
and occurrence of abnormal clinical test findings and side
effects whose relation to the study drug could not be ruled
out).

The selection criteria for this study were: essential hyper-
tension patients between 20 and 80 years of age attending
the outpatient clinic and patients from whom written in-
formed consent had been obtained to participate in the study.

The exclusion criteria were: 1) patients who had experi-
cenced the occurrence of an acute myocardial infarction,
stroke, or other vascular disease within the preceding 6
months, 2) patients who had a serious kidney disorder (ser-
rum creatinine value ≥2.0 mg/dL), 3) patients who had a se-
rious liver disorder [alanine aminotransferase (ALT) value 3
times the maximum value of the normal range or higher], 4)
patients who had bilateral renal artery stenosis, 5) secondary
hypertension patients, 6) malignant hypertension patients, 7)
pregnant or possibly pregnant patients, 8) patients who had
a history of hypersensitivity to the test drug, and 9) patients
judged by the physician in charge of the study to be inelig-
ible for any other reason.

The criteria for stopping the trial were: 1) a sharp in-
crease in BP (diastolic BP of 110 mmHg), 2) any manifesta-
tions of hypotension in the judgment of the attending physi-
cian (systolic BP <100 mmHg and/or diastolic BP <50
mmHg) or such symptoms as unsteadiness and/or feeling
dizzy upon standing, and 3) sharp fluctuations in the clinical
laboratory test values, including the serum creatinine and
potassium values. All study participants provided written in-
formed consent, and the Nihon University Surugadai Hospi-
tal Ethics Committee approved the study design and purpose
(approval number: 101103).

Selection and treatment of the trial subjects

Pre-observation period 1: The physician in charge of the
study selected patients as subjects when, according to the
clinic records, an antihypertensive drug(s) other than ali-
siren had been prescribed without any change in the
drug(s) during at least the preceding 2 months, but the mean
clinic BP on the most recent 2 visits had not reached the
target BP, and after explaining the nature of the study in
writing, the patient’s written consent to participate was ob-
tained.

Treatment period (pre-observation period 2): Home BP
measurements were made by using a home blood pressure
monitor with a memory card (EW-BU70, Panasonic Electric
Works, Tokyo, Japan) that had been designed for use in this
trial and obtained during the one-month and 6-month al-
siren administration period. When the clinic BP or home
BP measurements had not reached the target BP after one
month without changing any of the antihypertensive
drugs that had previously prescribed, the physician in charge
of the study added a prescription for aliskiren (150 mg once
daily). When the BP had not reached the target BP after a
one-month prescription for aliskiren, the dose of aliskiren was increased to 300 mg/day. When the BP after two months of prescribing a fixed dose of aliskiren reached the target BP, we decreased the amount of antihypertensive drugs other than aliskiren or stopped them and evaluated the clinic BP and home BP monthly. The class of drugs to decrease was left to the discretion of the attending physician.

Diabetes was defined as fasting plasma blood sugar concentrations ≥126 mg/dL and HbA1c ≥6.5% or current treatment with anti-diabetic agents. A diagnosis of dyslipidemia was made when the low-density lipoprotein cholesterol level was 140 mg/dL or above, the triglyceride level was 150 mg/dL or above, the high-density lipoprotein cholesterol level was less than 40 mg/dL, or if the patient was already on lipid-lowering agents. Smoking was defined as current smoking or smoking cessation within 1 year prior to the start of the study. CKD was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m².

**Measurement of BP**

BP was measured at the outpatient department at fixed times after the medications were administered. The BP measurement was carried out according to the JSH2009 guidelines (12). BP was measured monthly using a sphygmomanometer (Nippon Colin, Tokyo, Japan) in duplicate with the patient in a sitting position after a 5-minute rest. Subjects were instructed to measure their BP at home by making 2 measurements one minute apart after sitting at rest for 1-2 minutes within 1 hour after getting up, after voiding but before breakfast. The memory card was collected at each regularly scheduled clinic visit. The clinic and home BP values were evaluated by using the mean value of the BP values measured twice as that day’s BP values, and the mean monthly BP values were calculated.

**Measurement of the laboratory parameters**

Fasting blood samples were collected early in the morning after a 12-hour fast. The eGFR was calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) study formula modified by a Japanese coefficient (14).

**Statistical analysis**

We performed all statistical analyses using the SPSS Windows version 12.0 software program (Statistical Package for the Social Sciences, SPSS Ins., Chicago, USA). Data are expressed as the mean ± standard deviation (SD) for continuous variables. A comparison of the continuous variables was conducted using a paired t-test. To analyze changes in the BP, Dunnett’s multiple comparison was performed. To analyze changes in the serum creatinine, eGFR, and serum potassium levels, we used an analysis of variance (ANOVA). A p value less than 0.05 was considered to be statistically significant. Both the home and clinic BP values were subjected to univariate and multivariate logistic regression analyses as a means of identifying factors involved in achieving a target BP. Whether the target BP was achieved was used as a dependent variable, and age, gender, body mass index, whether 3 or more antihypertensive drugs were used, whether the subject had DM, and whether the subject had CKD were used as the independent variables.

**Results**

**Patient background**

The patient background factors are shown in Table 1. A total of 79 patients were enrolled in the trial. There were four dropouts from the trial: three patients stopped participating of their own accord, and one patient suffered from a cerebral infarction as a result of paroxysmal atrial fibrillation. Consequently, 75 patients were included in the final analyses.

**Target BP achievement rates and univariate and multivariate logistic regression analyses to identify predictors of target BP achievement**

The changes in BP during the course of the trial are shown in Fig. 1. The clinic BP and early-morning home BP values of the subjects overall were significantly lower than both the systolic and diastolic BP values at the time the subjects enrolled in the trial (Fig. 1a). The changes in BP of patients with DM as a complication and with CKD as a complication are shown in Fig. 1b and Fig. 1c, respectively. The target BP achievement rates of the patients enrolled overall and patients with DM as a complication and CKD as a complication calculated 6 months after the start of the trial are shown in Fig. 2. The univariate and multivariate logistic regression analyses identified an age of 65 years and older to be a significant independent predictor of achieving the target BP, and CKD was identified to be a significant inde-
Figure 1a. The overall change in BP. BP: blood pressure, SBP: systolic BP, DBP: diastolic BP, *
*p<0.05, vs. baseline; **p<0.0001, vs. baseline

Figure 1b. Change in the BP in patients with DM. BP: blood pressure, SBP: systolic BP, DBP: dias-
tolic BP, DM: diabetes mellitus, *
*p<0.05, vs. baseline; **p<0.0001, vs. baseline; ***p<0.001, vs. baseline

ependent predictor of failing to achieve the target BP (Ta-
ble 2).
Changes in the number of antihypertensive drugs taken

The mean number of drugs prescribed before the administration of aliskiren was 3.28±1.52; at 6 months, the mean number of drugs prescribed had decreased significantly to 2.85±1.72 (p <0.0001) (Fig. 3). Patients whose number of drugs or dose (subjects whose dose had been reduced even though the number of drugs had not) had been reduced accounted for 61% of the subjects as a whole. The details of the drugs that had been reduced in dose or number are shown in Fig. 4.

Changes in the clinical test values and the safety evaluation

Table 3 shows the changes in the clinical test values. No
significant changes in the serum creatinine values, e-GFR, or serum potassium values were observed during the trial period. Fig. 5 shows the changes the serum creatinine values, e-GFR, and serum potassium values in the diabetes and CKD cases during the trial period, in which ACEIs and ARBs were used in combination; however, none of the changes were significant (Fig. 5a and b). Moreover, no adverse events associated with excessive BP lowering, such as unsteadiness or dizziness on arising, were observed in relation to the addition of aliskiren.

Safety

No adverse events associated with excessive BP lowering, such as unsteadiness or dizziness on rising, were observed in relation to the addition of aliskiren. In addition, no abnormal changes in the laboratory measurements with or without possible causal relationship to the study medications during the study period were observed.

Discussion

We clarified the following points in this study. First, as a result of adding the direct renin inhibitor aliskiren to the treatment of hypertension patients who had not managed to reach their target BP with existing therapy, the patients’ home and clinic BP achievement rates improved, and it was possible to reduce the amount of antihypertensive drugs in approximately 60% of the participants in the trial overall. Second, the results also suggested that by carefully monitoring the renal function or reducing the amounts of drugs used in combination with aliskiren, aliskiren could be safely used without any worsening of the renal function even in patients with DM or CKD as a complication who were being treated with ACEIs/ARBs.

The fact that the mechanism of action of aliskiren leads to the inhibition of the entire RAAS system and that it is possible to obtain stable blood concentrations appears to be a major factor in obtaining the above results (7, 8). Because the pharmacological activity of aliskiren leads to improved target BP achievement rates despite reducing the amount of other antihypertensive drugs, it appears that aliskiren will become a very useful drug in clinical practice.

However, in the ALTITUDE trial (13), which used a double-blind method to compare the aliskiren-added group with the placebo group of high-risk type 2 diabetes patients who had cardiovascular disease and CKD, were taking ACEIs/ARBs, and had stable BP control, more adverse events, including cardiopulmonary arrest that required resuscitation, hypotension, hyperkalemia, and diarrhea, were observed in the aliskiren group, and the trial was stopped. As a result, the 2013 European Society of Hypertension/European Society of Cardiology (ESH/ESC) Guidelines for the Management of Hypertension advised against the use of aliskiren in combination with any RAAS system inhibitors (15).

In the present study, we assessed changes in the renal function of patients with DM or CKD as a complication who were taking ACEIs and ARBs in combination with aliskiren, however, favorable results were obtained in the target BP achievement rates in comparison with the previous reports, without observing any worsening of the renal function or the development of hyperkalemia in either group (3, 4). A major difference from the ALTITUDE trial (13) was that the subjects of the ALTITUDE trial were patients whose BP management had been previously adequately controlled, whereas the BP control by the existing therapy in the subjects of the present study was inadequate, and thus there was little possibility of inducing excessive BP lowering. The fact that we precisely monitored the changes in the renal

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**Table 2.** Univariate and Multivariate Logistic Regression Analysis to Identify Predictors of Target BP Achievement.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
</tr>
<tr>
<td>Male</td>
<td>1.042 0.339</td>
<td>9.285 1.797</td>
</tr>
<tr>
<td>BMI ≥25 (kg/m²)</td>
<td>0.926 0.304</td>
<td>0.975 0.304</td>
</tr>
<tr>
<td>Age ≥65 years</td>
<td>6.129 1.286</td>
<td>2.875 0.304</td>
</tr>
<tr>
<td>Number of drugs ≥3</td>
<td>0.500 0.168</td>
<td>0.129 0.031</td>
</tr>
<tr>
<td>DM</td>
<td>0.573 0.18</td>
<td>0.012 0.031</td>
</tr>
<tr>
<td>CKD</td>
<td>0.211 0.055</td>
<td>0.287 0.055</td>
</tr>
</tbody>
</table>

OR: odds ratio, CI: confidence interval. Abbreviations are as in Table 1.

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**Figure 3.** Changes in the number of drugs prescribed other than aliskiren.
function and BP of all of the patients and adjusted the administration of the antihypertensive drugs each time was a major factor in explaining this significant difference between the studies.

The multivariate regression analysis showed that being an elderly person, i.e., age 65 years or older, was an independent predictor of achieving the target BP. Schmieder et al. also showed that the depressor action of aliskiren increased in an age-dependent manner in patients 65 years of age and older in comparison with patients younger than 65 years of age (16). Their findings strongly support our own results. Aliskiren exerts an antihypertensive effect that is independent of the serum renin activity, and it is possible to obtain an adequate antihypertensive effect even in the elderly (17). Moreover, higher blood aliskiren concentrations have been reported to be maintained in the elderly compare with younger people (18). If the increases in aliskiren concentrations in the blood and antihypertensive effects are proportional, then that may explain the higher target BP achievement rate observed in the elderly patients.

Table 3. Changes in the Serum Creatinine, e-GFR, and Serum Potassium.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>2M</th>
<th>4M</th>
<th>6M</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Creatinine (mg/dL)</td>
<td>0.89 ± 0.25</td>
<td>0.90 ± 0.27</td>
<td>0.89 ± 0.24</td>
<td>0.89 ± 0.25</td>
<td>0.991</td>
</tr>
<tr>
<td>e-GFR (mL/min/1.73m²)</td>
<td>63.6 ± 14.3</td>
<td>64.1 ± 15.9</td>
<td>63.4 ± 13.8</td>
<td>62.1 ± 13.9</td>
<td>0.923</td>
</tr>
<tr>
<td>Serum Potassium (mEq/L)</td>
<td>4.3 ± 0.4</td>
<td>4.3 ± 0.3</td>
<td>4.3 ± 0.4</td>
<td>4.2 ± 0.4</td>
<td>0.542</td>
</tr>
</tbody>
</table>

Abbreviations are as in Table 1.

Figure 4. Details regarding the drugs that had been reduced in dose or number. ARB: angiotensin receptor blocker, ACEI: angiotensin-converting enzyme inhibitors, CCB: calcium channel blocker.

Figure 5a. Changes in the serum creatinine level, e-GFR, and serum potassium level in ARBs/ACEIs-treated patients with DM. e-GFR: estimated glomerular filtration rate, ARBs: angiotensin receptor blockers, ACEIs: angiotensin-converting enzyme inhibitors, DM: diabetes mellitus. Bold line indicates the mean value.
Figure 5b. Changes in the serum creatinine level, eGFR, and serum potassium level in ARBs/ACEIs-treated patients with CKD. eGFR: estimated glomerular filtration rate, ARBs: angiotensin receptor blockers, ACEIs: angiotensin-converting enzyme inhibitors, CKD: chronic kidney disease. Bold line indicates the mean value.

Trials of the antihypertensive effect and safety of aliskiren have been conducted in succession (19-23) following the ALTITUDE trial (13). The organ-protective effects of antihypertensive drugs are largely attributed to the decrease in BP, and aliskiren, which has a stable, 24-hour-long antihypertensive effect, appears to be useful for good BP management. In the future, we anticipate the performance of a clinical trial to demonstrate the usefulness of the organ-protective effect of aliskiren as well as its antihypertensive effect.

The adverse events associated with the addition of aliskiren to RAAS inhibitors include excessive hypotension, which was observed in approximately 12% of the patients in the aliskiren group in the ALTITUDE trial (13). This is caused by excessive blockade of the RAAS. The findings of the present study suggest that it may be better to reduce the dose of ACEIs/ARBs (which are RAAS inhibitor) from the viewpoint of safety, rather than that of other antihypertensive drugs, when reducing the amount of antihypertensive drugs used in combination with aliskiren in order to deal with the excessive blockade of the RAAS. Although the class of drugs whose dose was to be decreased was left to the discretion of the attending physician, the drug class that was selected by the largest number of physicians was ACEIs/ARBs, which may explain the absence of excessive hypotension in this study. When aliskiren was added to the treatment regimen of patients with poorly controlled BP who had already taken ACEIs/ARBs, it was essential to monitor the changes in BP carefully and gradually increase the dose of aliskiren, as we had specified in the protocol of this study.

Study limitations and clinical implication

There are several limitations associated with this study. First, when the drugs were decreased, the classes and doses of the drugs to decrease were left to the discretion of the attending physician, and no specific protocol was established. Second, an evaluation of compliance with the prescriptions of all of the drugs, including aliskiren, is needed. Third, although the addition of aliskiren to the existing drugs made it possible to reduce the amount of existing drugs used, the implication of the decrease in the number of drugs in relation to the amounts of the drugs taken as a result of aliskiren itself being added is a matter of controversy. It will be necessary to evaluate drugs that can be compared with aliskiren in future randomized trials. Finally, because this study was carried out before the publication of the results of the ALTITUDE trial (13), certain cases of DM and CKD received aliskiren. Moreover, as a result of careful monitoring of the renal function or decreasing the amounts of drugs used in combination, no worsening of the renal function was observed even in the cases complicated by diabetes or CKD being treated with ACEIs or ARBs, suggesting that aliskiren can be safely used.

Conclusion

Adding the direct renin inhibitor aliskiren to the treatment of hypertension patients who had not reached their target BPs improved the BP achievement rate, suggesting that it is possible to reduce the amount of antihypertensive drugs used in combination with aliskiren. Moreover, our results suggested that by carefully monitoring the renal function, making adjustments to the drugs used, and performing BP management, aliskiren can be safely used even in patients who are taking ACEIs/ARBs in combination to treat DM or CKD.

The authors state that they have no Conflict of Interest (COI).

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