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Effects of Aliskiren Monotherapy versus Amlodipine Monotherapy in Hypertensive Patients with Obesity or Type 2 Diabetes Mellitus

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Keywords
Hypertension · Renin · Renal function · Microalbuminuria

Abstract

Introduction: Renin-angiotensin system inhibitors have been reported to exert protective effects against organ damage and failure; however, the impact of the direct renin inhibitor as monotherapy has not been assessed. Here, we investigated the effects of 24-week monotherapy with aliskiren compared to amlodipine in hypertensive patients with type 2 diabetes or obesity. ***Methods:*** In this randomized intervention study, 62 adult hypertensive patients with visceral obesity (defined as a body mass index [BMI] greater than 25 kg/m^2 and a visceral adipose tissue area [VFA] greater than 100 cm^2) or type 2 diabetes mellitus (age 57 ± 13, 65% men, BMI 28.8 ± 4.8 kg/m^2, VFA 134.8 ± 47.0 cm^2, blood pressure 141 ± 16/86 ± 13 mm Hg) were randomized to receive 24-week treatment with aliskiren (max. 300 mg) or amlodipine (max. 10 mg). The primary outcome was the change in VFA at 24 weeks post-treatment. ***Results:*** Change in VFA did not differ significantly from baseline in either group. Systolic blood pressure significantly decreased at 12 weeks (−10 mm Hg, $p = 0.001$) and 24 weeks (−10 mm Hg, $p = 0.001$) in the amlodipine group and at 24 weeks (−11 mm Hg, $p = 0.001$) in the aliskiren group. Diastolic blood pressure significantly decreased at 24 weeks (−6 mm Hg, $p = 0.009$) only in the amlodipine group. Although the estimated glomerular filtration rates did not significantly change in either group, the logarithm of urinary albumin excretion significantly decreased at 24 weeks only in the aliskiren group (−0.60, $p < 0.001$). The 24-week changes in the urinary albumin excretion significantly correlated with the changes in the plasma renin activity in the aliskiren group ($r = 0.51$, $p = 0.008$). ***Conclusion:*** Aliskiren monotherapy did not show any superiority to amlodipine monotherapy on VFA, estimated glomerular filtration rates, or urinary albumin excretion in obese or type 2 diabetic hypertensive patients.

Introduction

Hypertension raises the risk of cardiovascular diseases and chronic kidney disease (CKD) [1], both of which contribute to increased mortality [2]. Many studies have demonstrated the importance of antihypertensive drugs that mechanistically inhibit the renin-angiotensin system (RAS) in preventing end-organ damage in hypertension. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) offer a blood

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pressure-independent reduction in proteinuria in both diabetic and non-diabetic CKD patients [3]. Therefore, they are generally accepted as first-line management of hypertension in patients with proteinuria and CKD [4].

There is a concern that treatment with ACE inhibitors and ARBs may cause increased renin activity, which has been reported as an independent predictor of major vascular events and mortality [5]. The direct renin inhibitor aliskiren has a long half-life and a long-term effect on lowering blood pressure [6], while simultaneously increasing renal plasma flow [7]. It has been reported that consumption of 300 mg of aliskiren daily decreases blood pressure in a similar manner to 100 mg of losartan daily [8]. Aliskiren-based antihypertensive treatment was reported to have a better effect on lowering blood pressure than ramipril-based treatment in the aliskiren for the geriatric lowering of systolic hypertension (AGELESS) study [9]. In addition, an in vivo study reported that aliskiren accumulated in the glomeruli and vasculatures of rat kidneys with high affinity [10], suggesting that aliskiren might have a renoprotective effect as well as a blood pressure-lowering effect. In the aliskiren evaluation of proteinuria in diabetes (AVOID) study [11], combination therapy with aliskiren and losartan significantly reduced urinary albumin excretion but not blood pressure more than losartan monotherapy in diabetic hypertensive patients. These results suggest a renoprotective effect of aliskiren, independent of its blood pressure-lowering effect.

RAS has been thought to affect body composition via its influence on the differentiation of pre-adipocytes to mature adipocytes; promotion of transcription of lipogenic enzymes, resulting in increased fatty acid synthesis and triglyceride storage; inhibition of lipolysis; and inhibition of adiponectin5 through angiotensin II type 1 receptor activation [12]. Indeed, ACE inhibitors and ARBs have been reported to decrease body weight in mice [13]. In addition, a few clinical studies have shown a decrease in visceral fat area (VFA) by ARBs [14]. Considering these facts, aliskiren may also have the potential to decrease body weight and VFA through interference with angiotensin II production. Because RAS is activated in obesity [15] and diabetes mellitus [16], aliskiren may have a better effect in patients with these conditions. However, since the failure of the aliskiren trial in type 2 diabetes using cardio-renal end-points (ALTITUDE) study [17], which showed no beneficial effect of aliskiren on cardiovascular and renal outcomes when added to ACE inhibitors or ARBs in diabetic and hypertensive patients, the role of aliskiren monotherapy has not been well investigated [18]. Herein, we conducted a prospective randomized trial to compare the effects of renin inhibitors and calcium channel blockers on visceral fat and renal function in hypertensive patients with obesity or diabetes.

Materials and Methods

Study Population

This prospective intervention study enrolled 75 adult patients with essential hypertension who were treated at the Tokyo Women's Medical University Hospital. Patients with an office systolic blood pressure of 140–160 mm Hg and an office diastolic blood pressure of 90–100 mm Hg with or without antihypertensive drugs and with either visceral obesity or type 2 diabetes mellitus were included in the study. Visceral obesity was defined as a body mass index (BMI) greater than 25 kg/m^2 and visceral adipose tissue area (VFA) greater than 100 cm^2. Type 2 diabetes was diagnosed according to the guidelines of the Japanese Diabetes Society [19]. Participants with the following medical history or condition were not enrolled: type 1 diabetes; hemoglobin A1c (HbA1c) (NGSP) greater than 9.0%; severe renal insufficiency defined as an estimated glomerular filtration rate (eGFR) lower than 30 mL/min/m^2; hyperkalemia with a potassium level of 5.5 mEq/L or higher; unstable angina; a recent history of myocardial infarction or stroke within 24 weeks; severe liver dysfunction; allergy to aliskiren, amlodipine, or doxazosin; being pregnant or nursing; and taking sodium-glucose co-transporter-2 inhibitors. Those who had been administered antihypertensive drugs, except amlodipine or doxazosin, for 4 weeks were also excluded.

Ethical Guidelines

The study was registered at the University Hospital Medical Information Network (UMIN000011865) and was conducted from October 2013 to December 2017. It was approved by the Ethics Committee of Tokyo Medical University Hospital (120903) with written informed consent from all participants.

Background Characteristics and Other Onsite Measurements

Background characteristics, including age, sex, past medical history, diagnosis, history of antihypertensive therapy, and smoking habits, were obtained from medical records. Height and body weight were measured using an automatic digital scale (AD-6228AP, A&D, Tokyo, Japan). Waist circumference (WC) was measured at the level of the umbilicus. The office blood pressure and pulse rate were measured at the outpatient clinic in a seated position. The first measurement at each visit was used in this study.

Blood and Urine Sample Collection

The blood of the participants was sampled after 30 min of rest in the supine position. Serum creatinine, cystatin C, uric acid, electrolytes including sodium, potassium, and chloride, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, high-sensitivity C-reactive protein (hsCRP), fasting plasma glucose, insulin, HbA1c, and brain natriuretic peptide levels were measured using standard laboratory assays. Plasma renin activity (PRA) and aldosterone concentration (PAC) were measured using radioimmunoassay. Serum pentraxin 3 level,

which is an inflammatory marker, was measured using the human PTX3 ELISA System (Perseus Proteomics, Tokyo, Japan).

Urinalysis, including pH, glucose, protein, creatinine, ketone body, albumin, sodium, and potassium, was performed using standard laboratory assays. Oxidative stress was assessed by measuring urinary 8-hydroxy-2′-deoxyguanosine (8-OHdG) using a new 8-OHdG Check ELISA kit (Japan Institute for the Control of Aging, Shizuoka, Japan).

Sodium intake was estimated using the Tanaka formula [20]. The eGFR estimated using serum creatine level (eGFRcre) was calculated using the formula: eGFRcre (mL/min/1.73 m^2) = 194 × creatinine (mg/dL) $^{(-1.094)}$ × age $^{(-0.287)}$ × 0.739 (if female) [21]. Whereas eGFR estimated using serum cystatin C level (eGFRcys) was calculated using the formula: eGFRcys (mL/min/1.73 m^2) = 104 × Cystatin C (mg/dL)$^{(-1.019)}$ × 0.996$^{(Age)}$ × 0.929 (if female) – 8 [22].

Measurement of Visceral Fat Area

VFA was measured by the dual bioelectrical impedance method using HDS-2000 DUALSCAN (Fukuda Colin, Tokyo, Japan), which was reported to be a non-invasive evaluation for VFA and has a high correlation with VFA determined by CT scan [23].

Evaluation of Atherosclerosis

The cardio-ankle vascular index (CAVI), a parameter of arterial stiffness independent of blood pressure [24], and ankle brachial index (ABI) were measured using the VaSera VS-1500AN (Fukuda Denshi, Tokyo, Japan). When the ABI was less than 0.9, the CAVI was not calculated. Arterial stiffness was also assessed using the augmentation index (AI), which is calculated by the amplitude of the early systolic pressure and late systolic pressure in the analysis of radial pulse waveform patterns [25], measured using HEM-9000AI (Omron Healthcare, Kyoto, Japan). Endothelial function was assessed by flow-mediated vasodilation (FMD) of the brachial artery using UNEX EF38G (UNEX Corporation, Nagoya, Japan).

Study Protocol

Participants were randomly divided into two groups: amlodipine and aliskiren. The participants of each group were restricted to using that particular drug; for example, those in the aliskiren group could only receive aliskiren. The target blood pressure was set to 130/80 mm Hg with some exceptions, such as 140/90 mm Hg in patients older than 65 years and patients with cerebrovascular disease, according to the 2009 hypertension guidelines by the Japanese Society of Hypertension (JSH) [26]. The initial doses were 2.5 mg once daily in the amlodipine group and 150 mg once daily in the aliskiren group, respectively. If antihypertensive therapy was insufficient, the dose of amlodipine or aliskiren was gradually increased to 10 and 300 mg/day, respectively, at the clinician's discretion. If required, only doxazosin was given additionally at a maximum dose of 8 mg/day. This treatment regime was continued for 24 weeks.

Each of the following measurements and tests were measured at the start of the treatment with follow-up at 12 and 24 weeks: anthropometry, blood pressure, blood and urine sample collection, and VFA. Pentraxin 3, 8-OHdG, FMD, AI, and CAVI were measured at the start and 24 weeks post-treatment.

The primary outcome of the study was the change in VFA at 24 weeks post-treatment. The secondary outcomes were as follows: (1) WC; (2) blood pressure and pulse rate; (3) renal function (eGFRcre, eGFRcys, and urinary albumin excretion); (4) atherosclerosis markers (CAVI, ABI, AI, and FMD); (5) oxidative marker (urinary 8-OHdG excretion); (6) inflammatory markers (serum pentraxin 3 and hsCRP levels); (7) adverse effects (hyperkalemia and hyperuricemia). Outcomes were also analyzed after dividing the participants into two subgroups: patients with and without diabetes.

Statistical Analyses

Statistical analyses were conducted using the JMP software (version 16.0; SAS Institute, USA). Data are represented as mean ± standard deviation or median (interquartile ranges) in descriptive analyses. Normality of the data was analyzed by visual inspection of Q-Q plots and histograms. For parameters with normal distribution, statistical significance between groups was calculated using the unpaired Student's *t* test. For parameters with skewed distribution, significance was assessed using the Mann-Whitney U test. Parameters with skewed distribution were log-transformed for subsequent analysis. To investigate the association between changes in urinary albumin excretion and systolic blood pressure, univariate regression analyses were performed using the Pearson correlation coefficient. Changes in continuous variables over time were analyzed using mixed-effects models for repeated measures in the SAS package (PROC MIXED) of SAS Studio (SAS Institute, USA). The statistical model included treatment, time, treatment-by-time interaction, and baseline values as fixed effects. An unstructured variance-covariance matrix was used to model within-patient error. The parameters were estimated using the restricted maximum likelihood estimation method, and the fixed effects were tested with the denominator degrees of freedom computed using the Kenward-Roger method. The least-squares mean was estimated for each treatment at each time point. The changes in least-squares means of the outcomes are presented as means with 95% confidence intervals (CI). Multiple comparisons of least-squares means of the outcomes were conducted between baseline, 12 and 24 weeks, and the two treatment groups at 24 weeks using the SAS pdiff option. Statistical significance was set at $p < 0.05$. In the multiple comparisons, $p < 0.017$ for pentraxin 3, 8-OHdG, and the markers of atherosclerosis and $p < 0.01$ for other parameters were used for statistical significance according to the Bonferroni correction applied by dividing the p value by the number of comparisons. We hypothesized that aliskiren would show superiority to amlodipine with regard to visceral fat area reduction in the study participants. We calculated that a sample of 72 participants would provide the trial with 90% power to show a significant treatment effect, with a standard deviation of 40 cm^2 and an estimated treatment difference of −30 cm^2. For the evaluation of all outcomes, the full analysis set was used, including all randomized subjects except those who did not satisfy major entry criteria (eligibility violations) or failed to take at least one dose of trial medication.

Results

Baseline Characteristics of the Study Participants

Of the participants, after excluding 3 patients in the amlodipine group and 7 patients in the aliskiren group, the subsequent analyses proceeded with 33 and 29 patients in each group, respectively (Fig. 1). The baseline characteristics of the 62 study participants are presented in Table 1.

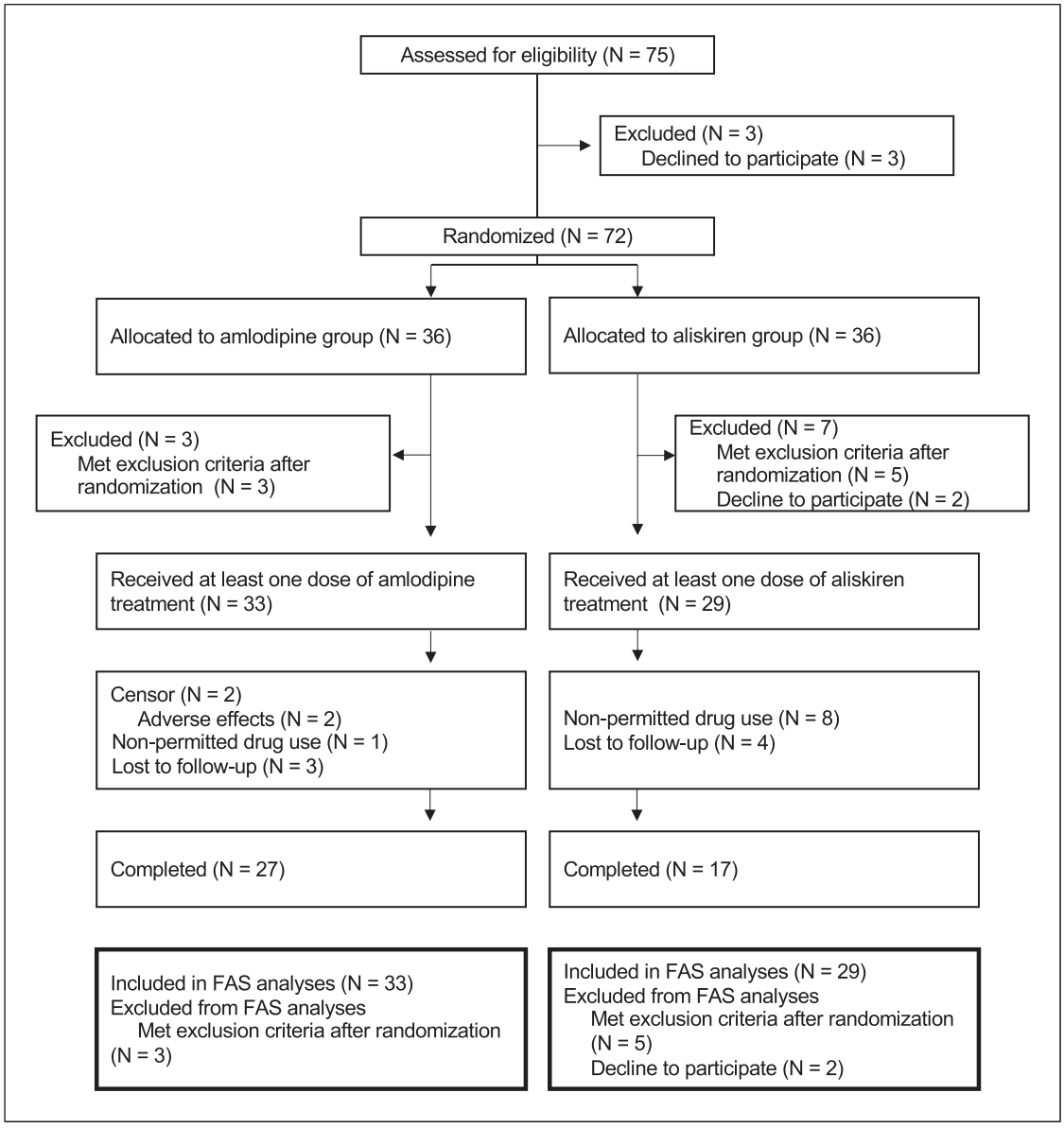

Fig. 1. Study disposition. FAS, full analysis set.

Dose Distribution Assessment of the Antihypertensive Drugs

At the end of the study, in the amlodipine group, the doses were distributed as 2.5 mg (N = 6), 5 mg (N = 7), 7.5 mg (N = 4), and 10 mg (N = 16), whereas the doxazosin dosage distribution was 2 mg (N = 2), 4 mg (N = 2), and 8 mg (N = 2). Similarly, for the aliskiren group, the doses were split as 150 mg (N = 15) and 300 mg (N = 14), with the doxazosin dosage distribution being 0.5 mg (N = 1) and 2 mg (N = 3). The doxazosin doses at the end of the study were not statistically different between the two groups (p = 0.54).

VFA and WC

VFA and WC were not significantly different from baseline at 12 or 24 weeks in the amlodipine or aliskiren groups (Table 2).

Table 1. Baseline characteristics of the study participants

	All (*N* = 62)	Amlodipine (*N* = 33)	Aliskiren (*N* = 29)	*p* value (amlodipine vs. aliskiren)
Age, years	57±13	57±13	56±13	0.69
Male, *N* (%)	40 (65)	18 (55)	22 (76)	0.112
BMI, kg/m^2	28.8±4.8	29.1±5.5	29.0±4.5	0.73
Waist circumference, cm	99.3±11.9	98.7±12.9	101.3±12.1	0.67
Visceral fat area, cm^2	134.8±47.0	128.8±45.7	147.6±54.9	0.30
Diabetes, *N* (%)	29 (47)	20 (61)	8 (28)	0.012
Dyslipidemia, *N* (%)	49 (79)	26 (79)	23 (79)	1.00
Systolic blood pressure, mm Hg	141±16	143±19	139±12	0.41
Diastolic blood pressure, mm Hg	86±13	86±13	86±13	0.96
Pulse rate, /min	73±10	74±11	72±10	0.50
Hemoglobin A1c (NGSP), %	6.3±0.9	6.6±0.9	6.0±0.8	0.004
Serum creatinine, mg/dL	0.78±0.17	0.76±0.17	0.79±0.15	0.29
eGFRcre, mL/min/1.73 m^2	75.2±15.0	75.1±16.1	76.3±13.5	0.99
eGFRcys, mL/min/1.73 m^2	85.8±18.2	84.5±19.6	88.0±16.5	0.52
Serum uric acid, mg/dL	5.9±1.3	5.8±1.4	5.9±1.2	0.81
Serum potassium, mEq/L	4.1±0.4	4.2±0.4	4.0±0.3	0.35
HDL cholesterol, mg/dL	50 (42–58)	51 (43–59)	48 (43–58)	0.49
LDL cholesterol, mg/dL	125 (105–145)	125 (100–146)	118 (103–141)	0.90
Triglyceride, mg/dL	134 (97–193)	113 (89–161)	140 (110–242)	0.056
PRA, ng/mL/h	1.2 (0.5–2.3)	1.1 (0.4–2.3)	1.5 (0.8–2.6)	0.133
PAC, pg/mL	156±78	152±80	158±76	0.64
Urinary albumin excretion, mg/gCr	13.6 (7.7–49.1)	15.6 (8.2–74.2)	13.4 (6.8–47.6)	0.41
Brain natriuretic peptide, pg/mL	10.7 (6.4–24.3)	13.2 (8.4–31.0)	9.1 (5.3–19.8)	0.094
hsCRP, ng/mL	1,110 (472–3,223)	1,230 (431–3,600)	1,150 (519–3,390)	0.89
Urinary 8-OHdG, ng/mL/gCr	11.5 (9.0–14.2)	11.7 (9.2–14.6)	10.7 (7.1–16.6)	0.26
Pentraxin 3, ng/mL	1.28 (0.98–1.72)	1.35 (0.96–2.01)	1.32 (0.99–1.61)	0.55
Estimated salt intake, g/day	9.2±2.1	9.4±2.2	8.9±2.2	0.47
Cardio-ankle vascular index	7.9±1.2	7.9±1.3	7.8±1.1	0.94
Ankle brachial pressure index	1.16±0.07	1.16±0.07	1.16±0.07	0.73
Flow-mediated dilation, %	4.7±1.8	4.7±1.7	4.6±1.9	0.80
Augmentation index, %	79±15	81±16	75±14	0.31

Data represent mean ± standard deviation or median (interquartile ranges). eGFRcre, eGFR calculated using serum creatinine level; eGFRcys, eGFR calculated using serum cystatin C level; HDL, high-density lipoprotein; LDL, low-density lipoprotein; 8-OHdG, 8-hydroxy-2′-deoxyguanosine.

Systolic and Diastolic Blood Pressures

Systolic blood pressure significantly decreased from baseline at 12 weeks (−10 [−15, −4] mm Hg, $p = 0.001$) and 24 weeks (−10 [−16, −4] mm Hg, $p = 0.001$) in the amlodipine group (Fig. 2a). In the aliskiren group, systolic blood pressure significantly decreased from baseline only at 24 weeks (−11 [−17, −5] mm Hg, $p = 0.001$). The changes in systolic blood pressure from baseline to 24 weeks were not significantly different between the two treatment groups ($p = 0.42$).

Diastolic blood pressure significantly decreased from baseline at 24 weeks (−6 [−10, −1] mm Hg, $p = 0.009$) but not at 12 weeks (−3 [−7, +1] mm Hg, $p = 0.14$) in the amlodipine group (Fig. 2b). In the aliskiren group, diastolic blood pressure did not significantly decrease from baseline at 12 (−2 [−7, +2] mm Hg, $p = 0.27$) or 24 weeks (−4 [−9, −0.1] mm Hg, $p = 0.046$). The changes in diastolic blood pressure from baseline to 24 weeks were not significantly different between the two groups ($p = 0.57$).

Renal Function and Urinary Albumin Excretion

Serum creatinine levels and eGFRcre did not significantly change from baseline at 12 or 24 weeks in the amlodipine or aliskiren group (Table 2). eGFRcys (Fig. 2c) did not significantly change from baseline at 12 weeks (−0.3 [−3.6, +2.9] mL/min/1.73 m^2, $p = 0.83$) or 24 weeks (−0.5 [−3.6, +2.6] mL/min/1.73 m^2, p =

Table 2. Changes in the markers of glucose metabolism, inflammation, oxidative stress, and renin-angiotensin-aldosterone system

	Changes from baseline				*p* value
	amlodipine		aliskiren		amlodipine vs. aliskiren
	12 weeks	24 weeks	12 weeks	24 weeks	24 weeks
Visceral fat area, cm^2	+0.1 [−0.1, +0.2] (p = 0.33)	+0.1 [−0.1, +0.2] (p = 0.36)	+0.0 [−0.1, +0.2] (p = 0.80)	+0.0 [−0.1, +0.2] (p = 0.76)	0.30
Waist circumference, cm	+1.4 [−0.5, +3.2] (p = 0.149)	−1.2 [−3.0, +0.6] (p = 0.198)	+1.0 [−0.9, +2.9] (p = 0.30)	+0.5 [−1.3, +2.3] (p = 0.58)	0.082
Serum creatinine, mg/dL	−0.01 [−0.05, +0.02] (p = 0.36)	+0.02 [−0.01, +0.05] (p = 0.19)	+0.02 [−0.01, +0.05] (p = 0.20)	+0.03 [+0.001, +0.06] (p = 0.043)	0.48
eGFRcre, mL/min/1.73 m^2	+1.6 [−1.6, +4.8] (p = 0.32)	−2.7 [−5.7, +0.4] (p = 0.091)	−1.2 [−4.4, +1.9] (p = 0.45)	−2.5 [−5.7, +0.7] (p = 0.120)	0.94
Hemoglobin A1c (NGSP), %	+0.1 [−0.1, +0.2] (p = 0.33)	+0.1 [−0.1, +0.2] (p = 0.36)	+0.0 [−0.1, +0.2] (p = 0.80)	+0.0 [−0.1, +0.2] (p = 0.76)	0.30
Logarithm of serum hsCRP	+0.1 [−0.3, +0.4] (p = 0.74)	−0.1 [−0.4, +0.3] (p = 0.61)	−0.2 [−0.5, +0.2] (p = 0.36)	−0.1 [−0.5, +0.3] (p = 0.51)	0.64
Logarithm of serum pentraxin 3	N.D.	+0.09 [−0.05, +0.23] (p = 0.21)	N.D.	−0.09 [−0.24, +0.06] (p = 0.23)	0.0166[a]
Logarithm of urinary 8-OHdG excretion	N.D.	−0.07 [−0.26, +0.12] (p = 0.48)	N.D.	+0.02 [−0.19, +0.23] (p = 0.85)	0.57
Logarithm of PRA	−0.01 [−0.35, +0.34] (p = 0.97)	−0.06 [−0.39, +0.27] (p = 0.70)	−1.31 [−1.65, −0.97] (p < 0.001*)	−1.42 [−1.76, −1.08] (p < 0.001*)	<0.001[a]
Plasma aldosterone, pg/mL	+29 [+5, +53] (p = 0.020)	+15 [−8, +38] (p = 0.021)	−33 [−57, −9] (p = 0.008*)	−27 [−51, +3] (p = 0.030)	0.003[a]
Flow-mediated vasodilation, %	N.D.	−0.4 [−1.1, +0.4] (p = 0.41)	N.D.	+0.3 [−0.4, +1.1] (p = 0.36)	0.080
Augmentation index, %	N.D.	−3 [−7, +1] (p = 0.109)	N.D.	−1 [−5, +4] (p = 0.80)	0.33
Cardio-ankle vascular index	N.D.	−0.15 [−0.48, +0.18] (p = 0.36)	N.D.	−0.19 [−0.54, +0.15] (p = 0.27)	0.79
Serum potassium, mEq/L	−0.1 [−0.2, +0.1] (p = 0.39)	+0.04 [−0.1, +0.2] (p = 0.57)	+0.1 [+0.01, +0.3] (p = 0.031)	+0.1 [+0.004, +0.3] (p = 0.044)	0.39
Serum uric acid, mg/dL	−0.3 [−0.5, +0.007] (p = 0.056)	−0.1 [−0.4, +0.1] (p = 0.31)	+0.2 [+0.1, +0.5] (p = 0.187)	+0.4 [+0.2, +0.7] (p = 0.003*)	<0.001[a]

Data represent least-squares means [95% confidence intervals]. eGFRcre, eGFR calculated using the serum creatinine level; hsCRP, high-sensitivity C-reactive protein; 8-OHdG, 8-hydroxy-2′-deoxyguanosine; N.D., no data. *Represents $p < 0.01$ versus baseline. [a]Represents $p < 0.01$ or $p < 0.017$ between the amlodipine group and the aliskiren group according to Bonferroni correction applied by dividing the p value by the number of comparisons.

0.77) in the amlodipine group and at 12 weeks (−2.1 [−5.3, +1.2] mL/min/1.73 m^2, p = 0.21) or 24 weeks (−2.3 [−5.6, +1.0] mL/min/1.73 m^2, p = 0.16) in the aliskiren group. The changes in eGFRcys from baseline to 24 weeks were not significantly different between the two groups (p = 0.37).

The logarithm of urinary albumin excretion at 12 weeks (+0.04 [−0.30, +0.31], p = 0.98) and 24 weeks (−0.21 [−0.50, +0.08], p = 0.16) did not significantly change from baseline in the amlodipine group (Fig. 2d). However, the logarithm of urinary albumin excretion at 24 weeks (−0.60 [−0.91, −0.30], $p < 0.001$), but not at 12 weeks (−0.14 [−0.43, +0.16], p = 0.37), significantly decreased from baseline in the aliskiren group. The changes in urinary albumin excretion from baseline to 24 weeks were not significantly different between the two groups (p = 0.025).

Glucose Metabolism, Inflammation, Oxidative Stress, Renin-Angiotensin-Aldosterone System, and Atherosclerosis Markers

Changes in HbA1c, FMD, AI, CAVI, and the logarithm of serum hsCRP, pentraxin 3, urinary 8-OHdG, PRA, and PAC during the treatment period are shown in Table 2. The logarithm of serum pentraxin 3 did not significantly change from baseline at 24 weeks in the amlodipine group (p = 0.21) or in the aliskiren group (p = 0.23). However, these changes were significantly different

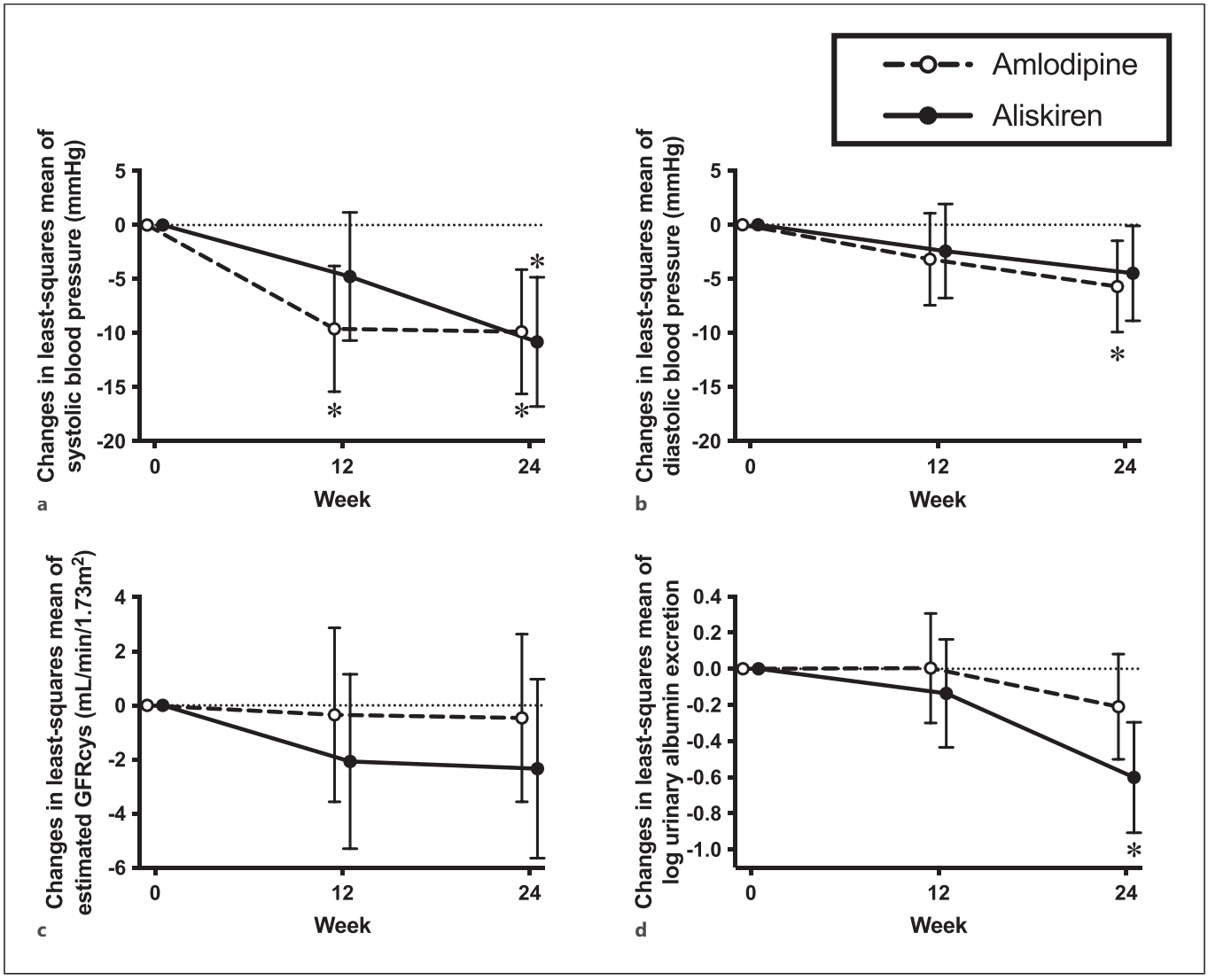

Fig. 2. Changes in blood pressure and kidney function such as systolic blood pressure (**a**), diastolic blood pressure (**b**), estimated glomerular filtration rate calculated using serum cystatin C level (eGFRcys) (**c**), and logarithm of urinary albumin excretion (**d**) during the 24-week treatment period. Open circles and dotted lines represent the amlodipine group, and closed circles and solid lines represent the aliskiren group. Error bars indicate 95% confidence intervals.

between the two groups (p = 0.0166). HbA1c and the logarithm of serum hsCRP at 12 weeks and at 24 weeks did not change from baseline in either group or between the two groups. Urinary 8-OHdG levels, FMD, AI, and CAVI values did not change from baseline at 24 weeks in either group or between the two groups.

The logarithm of PRA levels significantly decreased from baseline in the aliskiren group at 12 weeks (p < 0.001) and 24 weeks (p < 0.001), but not in the amlodipine group. Changes in the logarithm of PRA levels from baseline to 24 weeks were significantly different between the two groups (p < 0.001). The changes in PAC from baseline to 12 weeks, not 24 weeks, were significantly decreased in the aliskiren group (p = 0.008). The changes from baseline to 24 weeks were significantly different between the two groups (p = 0.003).

Impact of the Changes in Systolic Blood Pressure, PRA, and Pentraxin 3 on Urinary Albumin Excretion

The changes in the logarithm of urinary albumin excretion from baseline to 24 weeks did not significantly correlate with the changes in systolic blood pressure in the

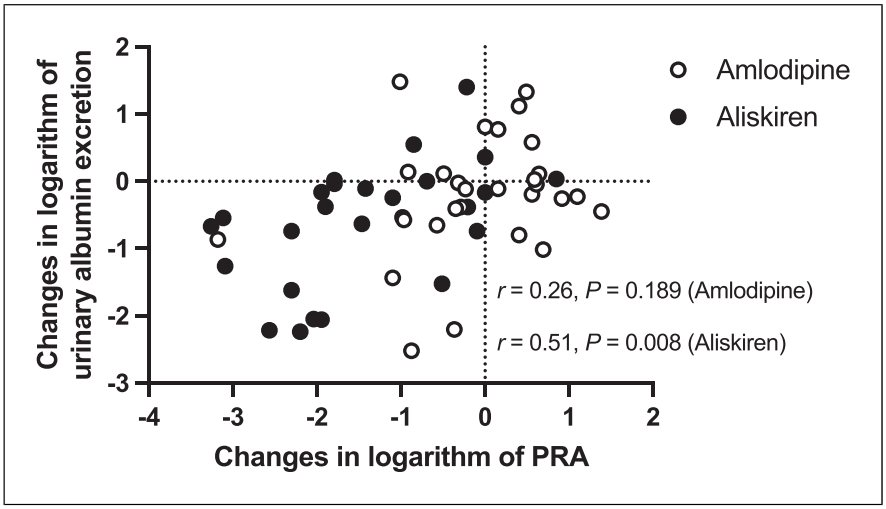

Fig. 3. Association between change in urinary albumin excretion and plasma renin activity (PRA) at 24 weeks. The open and closed circles represent the amlodipine and aliskiren groups, respectively. The changes in the logarithm of urinary albumin excretion from baseline to 24 weeks significantly correlated with the changes in the logarithm of PRA in the aliskiren group (r = 0.51, p = 0.008), but not in the amlodipine group (r = 0.26, p = 0.189).

amlodipine group (r = 0.31, p = 0.106) and the aliskiren group (r = 0.15, p = 0.47), respectively. However, they significantly correlated with the changes in the logarithm of PRA in the aliskiren group (r = 0.51, p = 0.008), but not in the amlodipine group (r = 0.26, p = 0.189) (Fig. 3). They did not significantly correlate with the changes in the logarithm of pentraxin 3 in the amlodipine group (r = 0.03, p = 0.86) and the aliskiren group (r = −0.25, p = 0.23), respectively.

Adverse Effects

Serum potassium levels did not differ significantly from baseline at 12 or 24 weeks in the amlodipine group and at 12 or 24 weeks in the aliskiren group, respectively (Table 2). Serum uric acid levels at 12 and 24 weeks in the amlodipine group did not significantly change from baseline (Table 2). However, the levels at 24 weeks (p = 0.003), but not at 12 weeks (p = 0.187), in the aliskiren group showed a significant increase from baseline. The changes in serum uric acid levels from baseline to 24 weeks were significantly different between the two groups (p < 0.001).

Subgroup Analyses of Patients with Diabetes

The participants were also subdivided into those with or without diabetes, with the background characteristics (online suppl. Table; for all online suppl. material, see https://doi.org/10.1159/000533834) and the outcomes (Table 3) as shown. Baseline BMI, waist circumference, and VFA were significantly higher in the non-diabetes subgroup than those in the diabetic subgroup. In both the diabetes and non-diabetes subgroups, PRA significantly decreased at 24 weeks in the aliskiren group. In patients with diabetes, WC, VFA, systolic and diastolic blood pressures, serum creatinine level, eGFRcre, eGFRcys, FMD, AI, and CAVI, along with logarithmic values of serum hsCRP, pentraxin 3 levels, urinary albumin, and 8-OHdG excretion, did not significantly change from baseline in either treatment group (Table 3).

In patients without diabetes, systolic blood pressure significantly decreased from baseline at 12 weeks (p = 0.003) and at 24 weeks (p < 0.001) in the amlodipine group, but only at 24 weeks (p < 0.001) in the aliskiren group (Table 3). The changes in systolic blood pressure from baseline to 24 weeks were not significantly different between the two groups (p = 0.52). Diastolic blood pressure did not change significantly in either group. Only the logarithm of urinary albumin excretion at 24 weeks in the aliskiren group significantly decreased from baseline (p < 0.001), without a significant difference between the two groups (p = 0.52).

The changes in the logarithm of urinary albumin excretion from baseline to 24 weeks in the aliskiren group significantly correlated with the changes in the logarithm of PRA in the non-diabetes subgroup (r = 0.54, p = 0.017) but not in the diabetes subgroup (r = 0.75, p = 0.053).

Discussion

In this randomized and prospective study, 24-week monotherapy with aliskiren did not result in significant changes in the VFA, which was examined as a primary outcome for obese or diabetic hypertensive patients, compared to amlodipine treatment. However, aliskiren treatment significantly decreased urinary albumin

Table 3. Changes in the outcomes in patients with or without diabetes

	Changes from baseline				*p* value
	amlodipine		aliskiren		amlodipine vs. aliskiren
	12 weeks	24 weeks	12 weeks	24 weeks	24 weeks
Diabetes subgroup (*N* = 28)					
Visceral fat area, cm^2	+11.3 [+1.4, +21.2] ($p = 0.027$)	−6.3 [−15.2, +2.6] ($p = 0.160$)	+7.7 [−7.1, +22.5] ($p = 0.30$)	+10.1 [+3.2, +23.4] ($p = 0.132$)	0.013
Waist circumference, cm	+1.7 [−0.8, +4.2] ($p = 0.179$)	−1.4 [−4.8, +1.0] ($p = 0.23$)	+0.5 [−3.1, +4.2] ($p = 0.77$)	+0.4 [−3.2, +3.9] ($p = 0.84$)	0.26
Systolic blood pressure, mm Hg	−7 [−15, +1] ($p = 0.082$)	−5 [−13, +2] ($p = 0.17$)	−7 [−19, +5] ($p = 0.26$)	−8 [−20, +4] ($p = 0.19$)	0.49
Diastolic blood pressure, mm Hg	−1 [−6, +5] ($p = 0.74$)	−6 [−11, 0] ($p = 0.035$)	−1 [−8, +9] ($p = 0.90$)	−2 [−10, +6] ($p = 0.51$)	0.49
Serum creatinine, mg/dL	−0.02 [−0.06, +0.02] ($p = 0.37$)	+0.03 [−0.01, +0.07] ($p = 0.125$)	+0.02 [−0.03, +0.08] ($p = 0.42$)	+0.03 [−0.02, +0.09] ($p = 0.25$)	0.75
eGFRcre, mL/min/1.73 m^2	+1.6 [−3.3, +6.5] ($p = 0.51$)	−3.8 [−8.4, +0.8] ($p = 0.106$)	−1.0 [−7.9, +6.0] ($p = 0.78$)	−3.4 [−10.4, +3.5] ($p = 0.33$)	0.98
eGFRcys, mL/min/1.73 m^2	−2.6 [−6.9, +1.6] ($p = 0.22$)	−0.3 [−4.2, +3.5] ($p = 0.86$)	−0.7 [−6.5, +5.1] ($p = 0.81$)	−0.2 [−6.2, +5.9] ($p = 0.96$)	0.95
Logarithm of urinary albumin excretion	+0.22 [−0.10, +0.54] ($p = 0.170$)	+0.05 [−0.24, +0.35] ($p = 0.72$)	+0.11 [−0.34, +0.56] ($p = 0.63$)	−0.04 [−0.50, +0.42] ($p = 0.86$)	0.70
Hemoglobin A1c (NGSP), %	+0.1 [−0.2, +0.4] ($p = 0.58$)	+0.1 [−0.2, +0.4] ($p = 0.48$)	+0.1 [−0.3, +0.5] ($p = 0.76$)	+0.1 [−0.3, +0.5] ($p = 0.62$)	0.55
Logarithm of serum hsCRP	−0.05 [−0.49, +0.39] ($p = 0.83$)	−0.14 [−0.55, +0.26] ($p = 0.48$)	−0.12 [−0.73, +0.50] ($p = 0.70$)	−0.19 [−0.83, +0.45] ($p = 0.55$)	0.99
Logarithm of serum pentraxin 3	N.D.	+0.20 [−0.03, +0.43] ($p = 0.092$)	N.D.	−0.17 [−0.52, +0.19] ($p = 0.35$)	0.022
Logarithm of urinary 8-OHdG excretion	N.D.	−0.15 [−0.28, +0.01] ($p = 0.030$)	N.D.	−0.11 [−0.32, +0.09] ($p = 0.28$)	0.88
Logarithm of PRA	+0.27 [−0.15, +0.69] ($p = 0.20$)	+0.23 [−0.16, +0.61] ($p = 0.24$)	−1.23 [−1.81, −0.65] ($p < 0.001$*)	−1.55 [−2.16, −0.95] ($p < 0.001$*)	<0.001[a]
Plasma aldosterone, pg/mL	+51 [+20, +83] ($p = 0.021$)	+28 [−1, +57] ($p = 0.057$)	+9 [−35, +53] ($p = 0.69$)	−6 [−52, +39] ($p = 0.78$)	0.077
Flow-mediated vasodilation, %	N.D.	−0.2 [−1.3, +0.9] ($p = 0.71$)	N.D.	+1.5 [−0.2, +3.1] ($p = 0.076$)	0.023
Augmentation index, %	N.D.	−2 [−6, +3] ($p = 0.47$)	N.D.	−2 [−10, +6] ($p = 0.58$)	0.81
Cardio-ankle vascular index	N.D.	+0.09 [−0.18, +0.36] ($p = 0.49$)	N.D.	−0.24 [−0.67, +0.18] ($p = 0.25$)	0.074
Non-diabetes subgroup (*N* = 34)					
Visceral fat area, cm^2	−6 [−20, +9] ($p = 0.44$)	+1 [−13, +15] ($p = 0.85$)	+5 [−6, +16] ($p = 0.37$)	−6 [−16, +4] ($p = 0.26$)	0.36
Waist circumference, cm	+1 [−2, +4] ($p = 0.55$)	−1 [−4, +2] ($p = 0.63$)	+1 [−1, +3] ($p = 0.30$)	+1 [−2, +3] ($p = 0.59$)	0.46
Systolic blood pressure, mm Hg	−13 [−21, −4] ($p = 0.003$*)	−17 [−25, −8] ($p < 0.001$*)	−4 [−10, +2] ($p = 0.22$)	−12 [−19, −5] ($p = 0.001$*)	0.52
Diastolic blood pressure, mm Hg	−6 [−13, 0] ($p = 0.068$)	−6 [−12, +1] ($p = 0.113$)	−4 [−9, +2] ($p = 0.184$)	−6 [−11, 0] ($p = 0.043$)	0.98
Serum creatinine, mg/dL	−0.01 [−0.06, +0.04] ($p = 0.68$)	+0.01 [−0.04, +0.06] ($p = 0.74$)	+0.02 [−0.02, +0.06] ($p = 0.34$)	+0.03 [+0.01, +0.07] ($p = 0.108$)	0.42
eGFRcre, mL/min/1.73 m^2	+1.6 [−2.7, +6.0] ($p = 0.46$)	−1.0 [−5.5, +3.5] ($p = 0.66$)	−1.3 [−4.7, +2.1] ($p = 0.45$)	−2.2 [−5.6, +1.3] ($p = 0.22$)	0.64
eGFRcys, mL/min/1.73 m^2	+2.1 [−3.0, +7.1] ($p = 0.41$)	−0.7 [−5.9, +4.4] ($p = 0.77$)	−2.7 [−6.7, +1.3] ($p = 0.187$)	−3.2 [−7.3, +0.9] ($p = 0.121$)	0.51
Logarithm of urinary albumin excretion	−0.25 [−0.74, +0.25] ($p = 0.32$)	−0.61 [−1.12, −0.10] ($p = 0.019$)	−0.23 [−0.61, +0.16] ($p = 0.24$)	−0.81 [−1.20, −0.41] ($p < 0.001$*)	0.52
Hemoglobin A1c (NGSP), %	+0.0 [−0.0, +0.1] ($p = 0.31$)	+0.0 [−0.1, +0.1] ($p = 1.00$)	+0.0 [−0.1, +0.1] ($p = 1.00$)	−0.0 [−0.1, +0.1] ($p = 0.78$)	0.82

Table 3 (continued)

	Changes from baseline				*p* value
	amlodipine		aliskiren		amlodipine vs. aliskiren
	12 weeks	24 weeks	12 weeks	24 weeks	24 weeks
Logarithm of serum hsCRP	+0.2 [−0.4, +8] (p = 0.51)	−0.0 [−0.6, +0.5] (p = 0.87)	−0.2 [−0.6, +0.3] (p = 0.40)	−0.1 [−0.5, +0.4] (p = 0.71)	0.74
Logarithm of serum pentraxin 3	N.D.	−0.07 [−0.23, +0.09] (p = 0.38)	N.D.	−0.06 [−0.19, +0.06] (p = 0.34)	0.91
Logarithm of urinary 8-OHdG excretion	N.D.	+0.1 [−0.3, +0.4] (p = 0.79)	N.D.	+0.1 [−0.2, +0.4] (p = 0.64)	0.95
Logarithm of PRA	−0.34 [−0.89, +0.20] (p = 0.22)	−0.52 [−1.07, +0.04] (p = 0.069)	−1.34 [−1.77, −0.92] (p < 0.001*)	−1.38 [−1.81, −0.95] (p < 0.001*)	0.003[a]
Plasma aldosterone, pg/mL	+2 [−34, +38] (p = 0.90)	−7 [−44, +30] (p = 0.71)	−50 [−78, −22] (p = 0.001*)	−36 [−64, −7] (p = 0.015)	0.15
Flow-mediated vasodilation, %	N.D.	−0.6 [−1.7, +0.4] (p = 0.24)	N.D.	−0.1 [−0.9, +0.7] (p = 0.82)	0.35
Augmentation index, %	N.D.	−6 [−12, +1] (p = 0.109)	N.D.	−0 [−6, +5] (p = 0.92)	0.138
Cardio-ankle vascular index	N.D.	−0.57 [−1.25, +0.10] (p = 0.094)	N.D.	−0.17 [−0.68, +0.33] (p = 0.49)	0.21

Data represent least-squares means [95% confidence intervals]. eGFRcre, eGFR calculated using the serum creatinine level; eGFRcys, eGFR calculated using the serum cystatin C level; hsCRP, high-sensitivity C-reactive protein; 8-OHdG, 8-hydroxy-2′-deoxyguanosine; N.D., no data. *Represents $p < 0.01$ versus baseline. [a]Represents $p < 0.01$ or $p < 0.017$ between the amlodipine group and the aliskiren group according to Bonferroni correction applied by dividing the p value by the number of comparisons.

excretion over 24 weeks, as a secondary outcome, although the change in urinary albumin excretion was not statistically different between the two treatment groups. Systolic and diastolic blood pressures, along with eGFR after the 24 weeks, were not statistically different between the treatment groups. The decrease in urinary albumin excretion was significantly correlated with the decrease in PRA. Although we could not conclude the superiority of aliskiren treatment, these results suggest a renoprotective effect of aliskiren monotherapy, independent of its blood pressure-lowering effect.

Our study suggests two characteristics of aliskiren monotherapy in the treatment of hypertension. First, inhibition of RAS by aliskiren monotherapy might have a renoprotective effect in hypertensive patients. Losartan therapy has shown better renal outcomes than amlodipine therapy in type 2 diabetic patients, although the antihypertensive effects of the two groups were similar [27]. This suggests the importance of RAS activation in renal damage. In our study, the participants had obesity and diabetes, which were reported to increase tissue RAS activity [15, 16]. The 24-week aliskiren treatment significantly decreased urinary albumin excretion, and the decrease in PRA was significantly correlated with the decrease in urinary albumin excretion. On the other hand, the 24-week amlodipine treatment did not significantly change urinary albumin excretion or PRA, although its blood pressure-lowering effect was not significantly different from that of the 24-week aliskiren treatment. Because the change in urinary albumin excretion was not statistically different between the two treatment groups, we cannot claim that the aliskiren treatment has a superior renoprotective effect over the amlodipine treatment. However, our data suggested that aliskiren treatment as a primary therapy might have a renoprotective effect independent of its blood pressure-lowering effect and dependent on its inhibitory effect of renin activity.

Second, aliskiren monotherapy might have a better effect in patients with obesity. In our study, the significant decrease in systolic blood pressure and urinary albumin excretion by the 24-week aliskiren therapy and the significant correlation between the decrease in urinary albumin excretion and PRA were observed only in the non-diabetes subgroup. BMI and VFA in the non-diabetes subgroup were significantly higher than those in the diabetes subgroup. A higher BMI is a significant variable when estimating the blood pressure-lowering effect of aliskiren [28]. Thus, obesity might have affected the blood pressure-lowering and renoprotective effect of aliskiren.

In addition, poorer medication adherence in diabetic patients [29] might have caused the lower efficacy in the diabetic subgroup.

These findings suggest the clinical usefulness of aliskiren monotherapy for the treatment of hypertension. The addition of aliskiren to ARB decreased urinary albumin excretion in hypertensive patients with type 2 diabetes in the AVOID study [11]. On the other hand, the addition of aliskiren to ACE inhibitors or ARB showed no desired effects with worse outcomes in hypertensive patients with type 2 diabetes, including a small number of patients with renal insufficiencies, in the ALTITUDE study [17]. The extremely strong RAS inhibition might be the causative agent for the worse outcomes observed in the study. In our study, aliskiren was used without other RAS inhibitors, with the dose titration done according to blood pressure and safety concerns. Furthermore, the aliskiren-induced reduction in urinary albumin excretion was only observed in non-diabetic patients in our study, thereby requiring further investigation into the renoprotective effects of aliskiren in non-diabetic hypertensive patients.

In the present study, body composition and markers of oxidative stress, endothelial function, and atherosclerosis were not different between the aliskiren and amlodipine treatment groups. Some studies have shown that RAS inhibitors may reduce body weight [13] and VFA [14]. Aliskiren has been reported to have an anti-inflammatory effect [30] and antioxidant activity [31]. These effects of RAS inhibitors on body composition, inflammation, and oxidative stress may be too small to be detected in clinical situations. In our study, the serum pentraxin 3 logarithmic values at 24 weeks were significantly lower in the aliskiren group than in the amlodipine group; however, those changes from baseline were not significant in both groups. The renoprotective effect of aliskiren could not be explained by changes in body composition, oxidative stress, or inflammation. Further studies are needed to clarify its mechanism.

In our study, aliskiren treatment did not show superiority of the outcomes except pentraxin 3 over amlodipine treatment. Amlodipine has a stable blood pressure-lowering effect independent of the RAS and has been used as a control in studies of the effects of many RAS inhibitors. However, only few studies compared aliskiren monotherapy to amlodipine monotherapy. Similar to our data, aliskiren monotherapy tended to show a lower, but not statistically significant, blood pressure-lowering effect compared to amlodipine monotherapy [32]. An umbrella review of systematic reviews also showed a significantly smaller blood pressure-lowering effect in aliskiren monotherapy compared to amlodipine monotherapy [33]. Regarding the study describing renoprotective effects, urinary albumin secretion was significantly decreased by aliskiren monotherapy, but not by amlodipine monotherapy, in hypertensive patients with CKD [34]. In the study, similar to our data, the change in urinary albumin excretion was not significantly different between the two treatment groups. Considering these results, a renoprotective effect of aliskiren monotherapy independent of its blood pressure-lowering effect might be too small to be detected.

Our study had some limitations. First, it included a small number of participants. Second, many patients were excluded from the analyses because they were initially incorrectly included in our study and then appropriately excluded during the randomization period. Third, antihypertensive therapies were titrated according to the JSH 2009 guidelines [26] in our study, which were the most recent guidelines when this study was planned. However, the impact of these guidelines on the study outcome is debatable as the current JSH 2019 guidelines [35] also propose a similar target blood pressure of 130/80 mm Hg. Finally, serum uric acid levels were significantly increased in the aliskiren group. Further studies are needed to assess the impact of aliskiren on serum uric acid levels.

In conclusion, 24-week aliskiren monotherapy did not show any superiority in altering the primary outcome of VFA or the secondary outcomes of blood pressure, eGFR, and urinary albumin excretion compared to 24-week amlodipine monotherapy in obese or diabetic patients with hypertension.

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Statement of Ethics

Written informed consent was obtained from all participants. This study was carried out in accordance with the Declaration of Helsinki. This study protocol was reviewed and approved by the Ethics Committee of Tokyo Medical University Hospital (120903).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors conceived and/or designed the work that led to the submission, revised the paper, approved the final version, and agreed to be accountable for all aspects of the work. Y.S., S.M., and K.B. carried out the data analyses, interpreted the data, did the literature search, and wrote the paper. Y.S. prepared the first draft of the manuscript. S.K., N.T., K.Y., K.B., N.S., D.W., and A.I. interpreted the data and made a significant contribution to the interpretation of the results.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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