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ORIGINAL ARTICLE

# Randomized trial of an increased dose of calcium channel blocker or angiotensin II type 1 receptor blocker as an add-on intensive depressor therapy in type 2 diabetes mellitus patients with uncontrolled essential hypertension: the ACADEMIE Study

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## Abstract

There is a lack of data on how to treat hypertensive patients with diabetes when treatment with medium doses of calcium channel blocker and angiotensin II type 1 receptor blocker (ARB) is insufficient to achieve the target blood pressure (BP). A total of 121 participants with type 2 diabetes and uncontrolled essential hypertension, who were receiving medium doses of amlodipine (5 mg/day) and ARB, were enrolled. Participants were randomized to receive either a high dose of amlodipine (10 mg/day) plus a medium dose of ARB (high-AML) or a medium dose of amlodipine (5 mg/day) plus a high dose of ARB (high-ARB). The depressor effects of these two regimens were monitored using a telemonitoring home BP-measuring system. Fifty-four patients were excluded after an observation period, and the remaining 67 eligible participants were randomized into the two groups; 42 which had a record of their home BP for analysis. The change in morning home systolic and diastolic BP was greater in the high-AML than in the high-ARB (systolic BP; −7.9 mmHg vs. +2.7 mmHg; $p=0.0002$, diastolic BP; −3.9 mmHg vs. +0.6 mmHg; $p=0.0007$). In addition, the home systolic and diastolic BP before going to bed and office systolic BP were significantly reduced from week 0 only in the high-AML. An increased dose of amlodipine, but not ARB, reduced home morning BP in hypertensive patients with type 2 diabetes who were already receiving combination therapy with medium doses of amlodipine and ARB.

**Keywords** Angiotensin II type 1 receptor blocker · Calcium channel blocker · Essential Hypertension · Home blood pressure · Type 2 diabetes mellitus

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## Introduction

Major cardiovascular risk factors include diabetes and hypertension. A vast majority of diabetes patients have a 10-year atherosclerotic cardiovascular disease (ASCVD) risk of more than 10%. The coexistence of diabetes and hypertension remarkably increases the likelihood of macrovascular and microvascular disease [1,2]. Among the participants in the Framingham study, patients with diabetes and hypertension exhibited higher rates of all-cause mortality and cardiovascular events than normotensive subjects with diabetes [3]. On the other hand, patients with diabetes often develop hypertension. In fact, the prevalence of hypertension in diabetic patients is higher than that in patients without diabetes; 50–80% of diabetic patients have hypertension [3–5].Several guidelines discuss the treatment strategy for hypertension with diabetes, including those that were recently released by the ACC/AHA [6]. The ACC/AHA guidelines recommended the use of antihypertensive drug treatment in patients with hypertension and diabetes at a blood pressure (BP) of 130/80 mmHg or higher with a treatment goal of less than 130/80 mmHg.

The renin-angiotensin system (RAS) is a key regulatory system of cardiovascular function and BP. Blockade of the RAS exerts protective effects on the cardiovascular system and renal function. Inhibitors of RAS, including angiotensin-converting enzyme (ACE) inhibitors and angiotensin II type 1 receptor blockers (ARBs), are first-line drugs for the treatment of hypertension. Although all major antihypertensive drug classes can be used to treat hypertension in diabetic patients, ACE inhibitors and ARBs are recommended as first-line drugs in many guidelines, especially in the presence of proteinuria and microalbuminuria [7,8]. Many clinical studies have demonstrated a significant reduction in the progression of albuminuria with the use of ACE inhibitors or ARBs [9,10].

Calcium channel blockers (CCBs) can also be used as first-line drugs in hypertension with diabetes, particularly in older patients [11]. The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-BPLA) showed that amlodipine-based treatment reduced the incidence of cardiovascular events compared to an atenolol-based regimen in patients with diabetes [12].

Thus, lowering BP in diabetic patients with hypertension is especially important. However, BP control is more difficult in patients with diabetes than in those without diabetes. It was reported that BP targets are achieved in only about 11% of diabetic patients, which is significantly lower than the rate in non-diabetic patients [13]. Therefore, we need to treat hypertension in diabetic patients more intensively than in non-diabetic patients, and proper therapeutic strategies need to be developed to treat these patients.

To achieve adequate BP control, most diabetic patients require combination therapy, and the combination of RAS blockers and CCBs has been recommended [14]. However, there is a lack of data for how to treat these patients when medium doses of ARBs and CCB are insufficient to achieve a target BP. In this study, to determine which anti-hypertensive therapy should be increased in these uncontrolled patients, we enrolled patients with type 2 diabetes who had not reached a target BP even though they were receiving combination therapy with medium doses of CCB (amlodipine) and ARB. These patients received an increased dose of CCB or ARB as an add-on intensive depressor therapy, and the depressor effects of these two therapies were monitored using an automated telemonitoring home BP-measuring system. In addition, the renal-protective and anti-inflammatory effects in the two groups were also examined.

## Methods

### Study design and population

ACADEMIE (An increased dose of CCB or ARB as an add-on intensive DEpressor therapy in type 2 diabetes MellItus patients with uncontrolled Essential hypertension) was a randomized controlled, multicenter clinical trial. The trial was undertaken in 16 centers in Japan, and was sponsored by Sumitomo Dainippon Pharma Co., Ltd. Participants were required to meet all the following criteria: diabetes according to the Japan Diabetes Society guidelines, essential hypertension with systolic BP ≥ 130 mmHg and/or diastolic BP ≥ 80 mmHg in an office setting, had been receiving a medium dose of amlodipine (5 mg/day) plus a medium dose of ARB for at least 4 weeks, and age 20 years or older. Exclusion criteria were as follows: secondary hypertension, systolic BP < 130 mmHg and diastolic BP < 80 mmHg in an office setting before allocation, severe liver dysfunction (AST or ALT, ≥ 2 times the upper limit of normal), severe renal dysfunction (serum creatinine ≥ 2.0 mg/dL), pregnancy or possibility of pregnancy in women, a history of allergy to any component of the study medications, contraindication for the study medications, participation in other clinical trials or within 3 months after retirement from a prior clinical trial, and ineligible based on the judgment of the physician. Written informed consent was obtained from all participants. The study was approved by the institutional review board at Fukuoka University School of Medicine (No. 15-11-06). The study is registered with the University Hospital Medical Information Network (UMIN) (UMIN000021594).

## Randomization and interventions

The study algorithms are shown in Fig. 1. Patients with hypertension and diabetes under treatment with amlodipine (5 mg/day) plus a medium dose of ARB were enrolled. Patients began to measure their home BP during the observation period before allocation. After a 4-week observation period, eligible participants were randomized to receive either amlodipine (10 mg/day) plus a medium dose of ARB (high-AML group) or a medium dose of amlodipine (5 mg/day) plus a high dose of ARB (high-ARB group) for 12 weeks. Treatment was open-label and participants continued to use the same kind of ARB after randomization. Randomization was stratified according to systolic BP in an office setting (systolic BP ≥ 140 mmHg, or systolic BP < 140 mmHg) and type of ARB. After randomization, the baseline antihypertensive regimens were changed on the basis of the study group assignment. All ARBs that can be prescribed in Japan were included (i.e., valsartan, candesartan, irbesartan, losartan, telmisartan, azilsartan, olmesartan). The ACADEMIE investigators could not change the antihypertensive drugs except for the increase in ARB or amlodipine at the time of allocation. After assignment, participants were seen every 4 weeks for 12 weeks. Adherence to treatment and concurrent drugs, including antiplatelet drugs and drugs for diabetes and dyslipidemia, were monitored prospectively throughout the trial.

## Study measurements

Patient characteristics were collected at baseline. Clinical data including concurrent drugs, BP in an office setting, laboratory data, and adverse events were obtained at baseline and every 4 weeks for 12 weeks. Office BP was measured twice and the average measurement was used. We used home BP monitoring to obtain a record of out-of-office BP. Daily measurement of home BP (morning BP, BP before going to bed) started after informed consent was obtained. Home BP was measured one to three times at each measurement session. Average home BP of the five days before each office visit was used for the analysis. BP while sleeping (BP two to three hours after going to bed) was measured two times daily (arbitrarily). BP measurements were obtained by using an automated measurement system (Model HEM-7252G-HP, Omron Healthcare). We used a telemonitoring system (i.e., automated data-transfer system) for home BP measurement, with which BP readings were automatically relayed to the study server. Serious adverse events were defined as events that resulted in death, were life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, or which resulted in persistent or significant disability or incapacity, or a congenital anomaly or birth defect in offspring.

## Study outcomes

The primary outcome measure was the change in morning home systolic BP from week 0 to week 12. Secondary

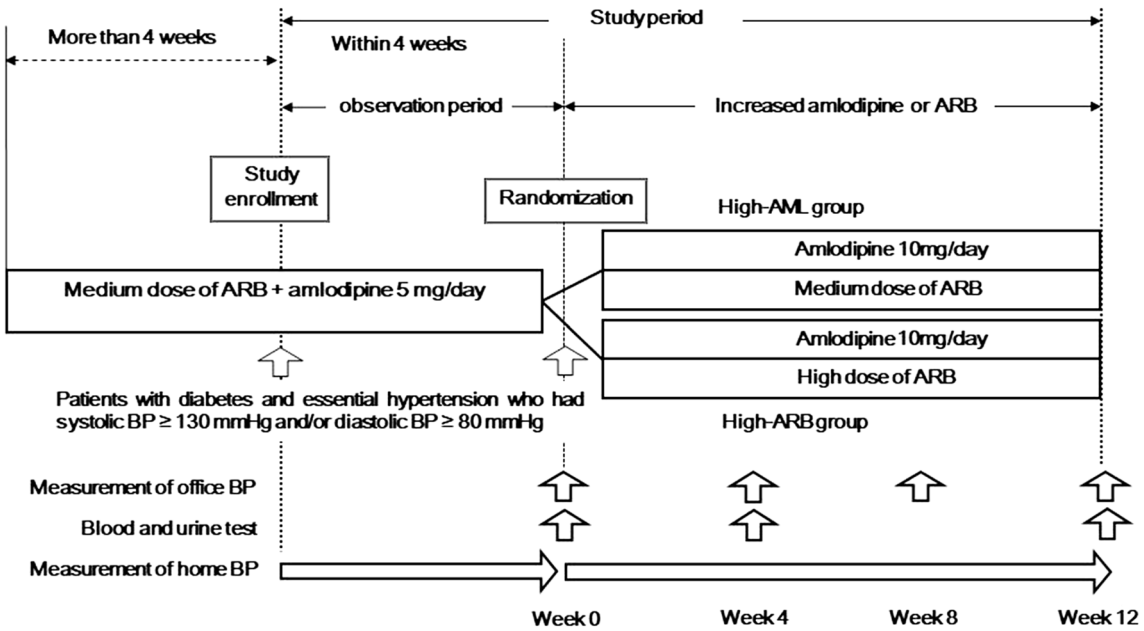


**Fig. 1** Study algorithms. *BP* blood pressure, *AML* amlodipine, *ARB* angiotensin II type 1 receptor blocker

outcomes included adverse events and changes in the following items from week 0 to week 12: morning home diastolic BP, BP in an office setting, home BP before going to bed, nighttime BP while asleep, achievement rate of target BP (< 130/80 mmHg in office BP and < 125/75 mmHg in morning home BP), variation of BP (standard deviation, SD) and variability index of BP (coefficient of variation, CV:SD/mean value), brachial-ankle pulse wave velocity (baPWV), plasma levels of pentraxin 3 and brain natriuretic peptide (BNP), serum levels of high sensitive C-reactive protein (hs-CRP) and adiponectin, urinary albumin, cystatin C, and L-type fatty acid binding protein (L-FABP). A prespecified subgroup analysis was performed based on baseline systolic BP in an office setting (systolic BP ≥ 140 mmHg, or systolic BP < 140 mmHg) and type of ARB. Adverse events were analyzed with a safety analysis population comprised of participants who had received the increased amount of amlodipine or ARB at least once.

### Statistical analysis

Based on the Amlodipine Versus Angiotensin II Receptor Blocker, Control of Blood Pressure Evaluation Trial in Diabetics (ADVANCED-J) study [15] and PRINCE10 study [16], we assumed that the change in systolic BP from week 0 to week 12 between two groups would be about − 9.5 mmHg and the standard deviation would be 16.7 mmHg. Since we anticipated losing 20% of the participants to follow-up, with an enrollment target of 120 participants, this trial would have 80% power to detect a significant difference in the primary outcome. Data are presented as the mean ± SD. Changes were calculated as the value at week 12 – value at week 0. Change in BP at week 12 was compared between the two groups using Analysis of Variance (ANOVA). Repeated measurement data were analyzed using Mixed-Effect Model for Repeated Measurement (MMRM). Multiplicity was adjusted by Dunnett's method and the Bonferroni method case by case. The level of statistical significance was 0.05. Analyses were performed using SAS software, version 9.3 (SAS Institute).

## Results

### Characteristics of the study participants.

A total of 121 participants were enrolled. Fifty-four patients were excluded due to the exclusion criteria after the observation period, and the remaining 67 eligible participants were randomized to receive either a high dose of amlodipine (10 mg/day) plus a medium dose of ARB (high-AML group) or a medium dose of amlodipine (5 mg/day) plus a high dose of ARB (high-ARB group) (Figs. 1, 2). Forty-two of these 67 participants had a record of home BP for analysis. The baseline characteristics of the study participants are presented in Table 1. There were no differences in the baseline characteristics between the two groups except for age and the usage of thiazide and a loop diuretic. The mean age of the participants was 69.8 years, 71.4% were male and 45.2% had a smoking history. Average systolic BP

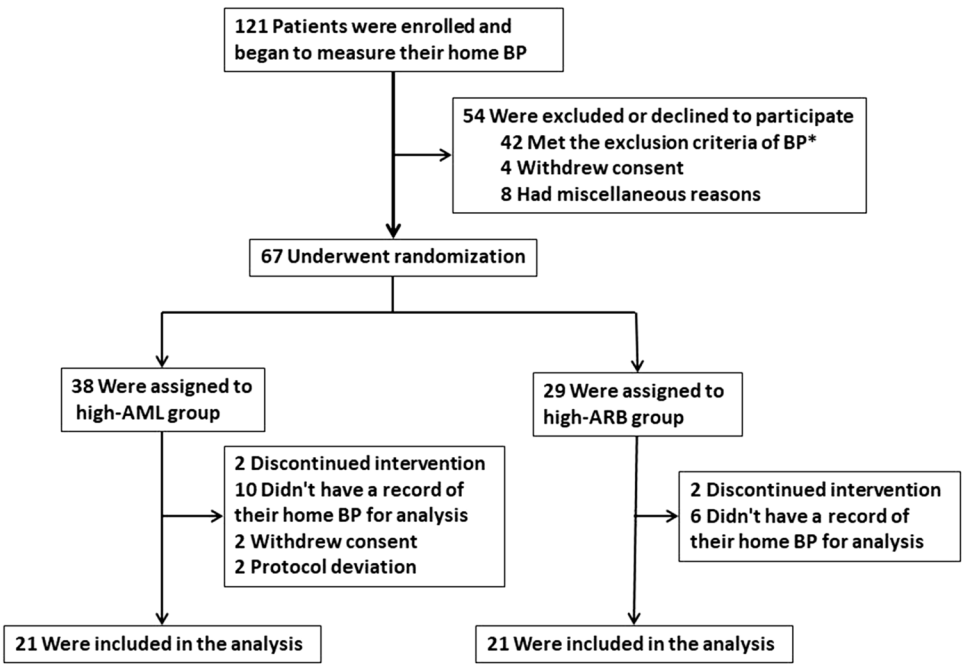


**Fig. 2** Eligibility, randomization, and follow-up. *Systolic BP < 130 mmHg and diastolic BP < 80 mmHg in an office setting

**Table 1.** Characteristics of the participants at baseline

| | Overall ($n=42$) | High-AML ($n=21$) | High-ARB ($n=21$) | $p$ value |
|---|---|---|---|---|
| Age-years | 69.8 ± 11.14 | 73.2 ± 9.17 | 66.4 ± 12.09 | 0.046 |
| 20 <= < 60 | 11 (26.2) | 4 (19.0) | 7 (33.3) | 0.390 |
| 60 <= < 75 | 15 (35.7) | 7 (33.3) | 8 (38.1) | |
| 75<= | 16 (38.1) | 10 (47.6) | 6 (28.6) | |
| Male sex-no. (%) | 30 (71.4) | 14 (66.7) | 16 (76.2) | 0.495 |
| BMI (kg/m$^2$) | | | | |
| < 25 | 16(38.1) | 5(23.8) | 11(52.4) | 0.157 |
| 25<= < 30 | 19(45.2) | 12(57.1) | 7(33.3) | |
| 30 <= | 7(16.7) | 4(19.0) | 3(14.3) | |
| Smoking status-no. (%) | | | | |
| Never smoked | 23 (54.8) | 14 (66.7) | 9 (42.9) | 0.297 |
| Current smoker | 5 (11.9) | 2 (9.5) | 3 (14.3) | |
| Former smoker | 14 (33.3) | 5 (23.8) | 9 (42.9) | |
| Unkown | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| Drinking history-no. (%) | | | | |
| No | 21 (50.0) | 10 (47.6) | 11 (52.4) | 0.758 |
| Yes | 21 (50.0) | 11 (52.4) | 10 (47.6) | |
| Unknown | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| Previous medical history-no. (%) | | | | |
| None | 31 (73.8) | 16 (76.2) | 15 (71.4) | 0.726 |
| Missing data | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| Yes | 11 (26.2) | 5 (23.8) | 6 (28.6) | |
| Dyslipidemia | 28 (66.7) | 15 (71.4) | 13 (61.9) | 0.513 |
| Cardiovascular disease | 10 (23.8) | 4 (19.0) | 6 (28.6) | 0.469 |
| Chronic kidney disease | 3 (7.1) | 1 (4.8) | 2 (9.5) | 0.549 |
| ARB at baseline-no. (%) | | | | |
| Valsartan | 4(9.5) | 3(14.3) | 1(4.8) | 0.747 |
| Candesartan | 5(11.9) | 3(14.3) | 2(9.5) | |
| Irbesartan | 3(7.1) | 2(9.5) | 1(4.8) | |
| Losartan | 7(16.7) | 4(19.0) | 3(14.3) | |
| Telmisartan | 13(31.0) | 5(23.8) | 8(38.1) | |
| Azilsartan | 9(21.4) | 4(19.0) | 5(23.8) | |
| Olmesartan | 1(2.3) | 0(0.0) | 1(4.8) | |
| Medication at baseline-no. (%) | | | | |
| No | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| Yes | 42 (100.0) | 21 (100.0) | 21 (100.0) | |
| Antidiabetic drug-no. (%) | 32 (76.2) | 15 (71.4) | 17 (81.0) | 0.469 |
| Biguanide | 7 (16.7) | 3 (14.3) | 4 (19.0) | 0.679 |
| Thiazolidinedione | 2 (4.8) | 1 (4.8) | 1 (4.8) | 1.000 |
| Sulfonylurea | 8 (19.0) | 3 (14.3) | 5 (23.8) | 0.432 |
| Glinide | 2 (4.8) | 0 (0.0) | 2 (9.5) | 0.147 |
| DPP-4 inhibitor | 30 (71.4) | 14 (66.7) | 16 (76.2) | 0.495 |
| α-glucosidase inhibitor | 7 (16.7) | 3 (14.3) | 4 (19.0) | 0.679 |
| SGLT2 inhibitor | 3 (7.1) | 1 (4.8) | 2 (9.5) | 0.549 |
| Insulin | 4 (9.5) | 2 (9.5) | 2 (9.5) | 1.000 |
| Lipid-lowering drug-no. (%) | 30 (71.4) | 15 (71.4) | 15 (71.4) | 1.000 |
| Statin | 28 (66.7) | 15 (71.4) | 13 (61.9) | 0.513 |
| Fibrate | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| EPA, EPA/DHA | 8 (19.0) | 3 (14.3) | 5 (23.8) | 0.432 |
| Ezetimibe | 1 (2.4) | 1 (4.8) | 0 (0.0) | 0.312 |
| Others | 0 (0.0) | 0 (0.0) | 0 (0.0) | |

**Table 1.** (continued)

| | Overall ($n=42$) | High-AML ($n=21$) | High-ARB ($n=21$) | $p$ value |
|---|---|---|---|---|
| Antihypertensive drug-no. (%) | 20 (47.6) | 13 (61.9) | 7 (33.3) | 0.064 |
| Loop diuretic | 7 (16.7) | 6 (28.6) | 1 (4.8) | 0.038 |
| Aldosterone antagonist | 3 (7.1) | 1 (4.8) | 2 (9.5) | 0.549 |
| Thiazide | 5 (11.9) | 5 (23.8) | 0 (0.0) | 0.017 |
| β blocker (αβ blocker) | 15 (35.7) | 8 (38.1) | 7 (33.3) | 0.747 |
| α blocker | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| ACE inhibitor | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| Others | 0 (0.0) | 0 (0.0) | 0 (0.0) | |

Data are mean (SD) or number (%).

*BMI* body mass index, *ARB* Angiotensin II type 1 receptor blocker, *DPP-4 inhibitor* dipeptidyl peptidase-4 inhibitor, *SGLT2 inhibitor* sodium-glucose cotransporter 2 inhibitor, *EPA* eicosapentaenoic acid, *DHA* docosahexaenoic acid, *ACE inhibitor* angiotensin-converting enzyme (ACE) inhibitor.

in an office setting at baseline, when the participants were randomized, was 145 ± 12 mmHg in the high-AML group and 143 ± 10 mmHg in the high-ARB group.

## Changes in home and office BP

Changes in BP are shown in Table 2. Although both groups received an increased amount of antihypertensive drug, only the high-AML group showed a rapid reduction of systolic BP. The change in morning home systolic BP from week 0 to week 12 was -7.9 ± 8.9 mmHg in the high-AML group ($p=0.0004$ vs. week 0) and +2.7 ± 9.9 mmHg in the high-ARB group ($p=0.303$ vs. week 0) (high-AML vs. high-ARB, $p=0.0002$) (Fig. 3). The difference between the high-AML and high-ARB groups was significant beginning 8 weeks after randomization ($p=0.005$). We performed the same analysis with a Per Protocol Set (PPS), in which participants who used loop diuretics or a sodium-glucose cotransporter 2 (SGLT2) inhibitor after enrollment were excluded, and reached a similar result; i.e., there was a significant difference in the change in morning home systolic BP between the groups (high-AML group − 7.9 ± 9.4 mmHg vs. high-ARB group +3.5 ± 10 mmHg, $p=0.0003$).

The change in morning home diastolic BP was − 3.9 ± 4.5 mmHg in the high-AML group ($p=0.001$ vs. week 0) and +0.6 ± 3.9 mmHg in the high-ARB group ($p=0.738$ vs. week 0) (high-AML vs. high-ARB, $p=0.0007$). Although the changes in home systolic and diastolic BP before going to bed were also significantly reduced in the high-AML group (systolic BP − 4.9 ± 9.8 mmHg, $p=0.025$ vs. week 0, diastolic BP − 3.0 ± 5.9 mmHg, $p=0.034$ vs. week 0), but not in the high-ARB group (systolic BP − 0.5 ± 9.1 mmHg, $p=0.964$ vs. week 0, diastolic BP − 1.6 ± 4.7 mmHg, $p=0.399$ vs. week 0), there were no significant differences between the two groups. The change in office systolic BP from week 0 to week 12 was − 13.9 ± 11.8 mmHg in the high-AML group ($p<0.0001$ vs. week 0) and − 5.6 ± 13.0 mmHg in the high-ARB group ($p=0.101$ vs. week 0) (high-AML vs. high-ARB, $p=0.013$) (Fig. 4).

The target morning home systolicss BP (systolic BP < 125 mmHg and diastolic BP < 75 mmHg) was achieved at week 12 in 22.2% of the patients in the high-AML group ($p=0.023$ vs. week 0) and in 10.0% of those in the high-ARB group ($p=0.959$ vs. week 0) (high-AML vs. high-ARB, $p=0.302$). The target office BP (systolic BP < 130 mmHg and diastolic BP < 80 mmHg) was achieved at week 12 in 36.8% of the patients in the high-AML group ($p=0.002$ vs. week 0) and in 20.0% of those in the high-ARB group ($p=0.031$ vs. week 0) (high-AML vs. high-ARB, $p=0.243$).

## Other outcomes

Except for the above-mentioned BP data, there were no differences in secondary outcomes related to BP between the high-AML and the high-ARB groups, including the variation of BP (SD) and an index of the variability of BP (CV) (data not shown). We didn't have enough data regarding nighttime BP while sleeping, baPWV or urinary cystatin C for a statistical analysis. As shown in Table 3, there were no differences in markers of kidney damage, i.e., urinary albumin and L-FABP. There were also no differences in inflammatory markers, such as hs-CRP and pentraxin 3. However, serum adiponectin levels were significantly increased only in the high-ARB group: +0.37 ± 1.45 μg/mL in the high-AML group ($p=0.262$ vs. week 0) and +0.58 ± 1.26 μg/mL in the high-ARB group ($p=0.026$ vs. week 0). There was no difference in the change in the serum level of adiponectin between the two groups (high-AML vs. high-ARB, $p=0.404$). As shown in Table 4, there were no differences in glucose or lipid profiles except for hemoglobin A1c (HbA1c) and LDL cholesterol (LDL-C). The change in HbA1c was + 0.03 ± 0.36% in the high-AML group and − 0.25 ± 0.80% in the high-ARB group

**Table 2.** Change in BP

| | Week 0 Mean ± SD (*n*) | Week 4 Mean ± SD (*n*) | Week 8 Mean ± SD (*n*) | Week 12 Mean ± SD (*n*) | Week 0 vs. week 12 | CCV vs. ARB |
|---|---|---|---|---|---|---|
| Morning home systolic BP (mmHg) | | | | | | |
| High-AML | 144 ± 13 (21) | 139 ± 13 (21) | 136 ± 10 (19) | 135 ± 13 (18) | | |
| High-ARB | 136 ± 11 (21) | 136 ± 11 (21) | 137 ± 13 (19) | 138 ± 14 (20) | | |
| Change in morning home systolic BP (mmHg) | | | | | | |
| High-AML | | − 4.3 ± 7.8 (21) | − 7.8 ± 10.1 (19) | − 7.9 ± 8.9 (18) | 0.0004 | 0.0002 |
| High-ARB | | 0.6 ± 6.5 (21) | 1.9 ± 10.1 (19) | 2.7 ± 9.9 (20) | 0.3033 | |
| Morning home diastolic BP (mmHg) | | | | | | |
| High-AML | 82 ± 8 (21) | 79 ± 6 (21) | 77 ± 6 (19) | 78 ± 8 (18) | | |
| High-ARB | 79 ± 10 (21) | 80 ± 10 (21) | 79 ± 10 (19) | 80 ± 10 (20) | | |
| Change in morning home diastolic BP (mmHg) | | | | | | |
| High-AML | | − 3.1 ± 4.9 (21) | − 5.2 ± 4.9 (19) | − 3.9 ± 4.5 (18) | 0.0013 | 0.0007 |
| High-ARB | | 1.0 ± 4.2 (21) | 0.4 ± 4.5 (19) | 0.6 ± 3.9 (20) | 0.7377 | |
| Home systolic BP before going to bed (mmHg) | | | | | | |
| High-AML | 133 ± 12 (21) | 130 ± 11 (20) | 129 ± 13 (18) | 129 ± 15 (18) | | |
| High-ARB | 130 ± 12 (21) | 130 ± 12 (21) | 127 ± 15 (19) | 129 ± 12 (20) | | |
| Change in home systolic BP before going to bed (mmHg) | | | | | | |
| High-AML | | − 3.8 ± 6.7 (20) | − 4.7 ± 8.0 (18) | − 4.9 ± 9.8 (18) | 0.0247 | 0.1519 |
| High-ARB | | 0.6 ± 10.3 (21) | − 2.7 ± 11.7 (19) | − 0.5 ± 9.1 (20) | 0.9641 | |
| Home diastolic BP before going to bed (mmHg) | | | | | | |
| High-AML | 75 ± 8 (21) | 74 ± 7 (20) | 73 ± 7 (18) | 73 ± 7 (18) | | |
| High-ARB | 75 ± 10 (21) | 75 ± 10 (21) | 72 ± 11 (19) | 73 ± 9 (20) | | |
| Change in home diastolic BP before going to bed (mmHg) | | | | | | |
| High-AML | | − 2.6 ± 5.4 (20) | − 2.9 ± 5.0 (18) | − 3.0 ± 5.9 (18) | 0.0343 | 0.4352 |
| High-ARB | | 0.6 ± 6.5 (21) | − 2.2 ± 5.9 (19) | − 1.6 ± 4.7 (20) | 0.3989 | |
| Office systolic BP (mmHg) | | | | | | |
| High-AML | 145 ± 12 (21) | 132 ± 14 (20) | 129 ± 13 (19) | 131 ± 13 (19) | | |
| High-ARB | 143 ± 10 (21) | 135 ± 13 (21) | 142 ± 14 (19) | 138 ± 15 (20) | | |
| Change in office systolic BP (mmHg) | | | | | | |
| High-AML | | − 12.4 ± 11.5 (20) | − 15.6 ± 11.3 (19) | − 13.9 ± 11.8 (19) | <0.0001 | 0.013 |
| High-ARB | | − 8.1 ± 11.7 (21) | − 2.3 ± 12.6 (19) | − 5.6 ± 13.0 (20) | 0.1014 | |
| Office diastolic BP (mmHg) | | | | | | |
| High-AML | 74 ± 9 (21) | 72 ± 7(20) | 67 ± 9 (19) | 70 ± 8 (19) | | |
| High-ARB | 79 ± 12 (21) | 73 ± 12 (21) | 76 ± 12 (19) | 76 ± 11 (20) | | |
| Change in office diastolic BP (mmHg) | | | | | | |
| High-AML | | − 1.9 ± 6.7 (20) | − 6.5 ± 7.0 (19) | − 4.0 ± 9.1 (19) | 0.0559 | 0.2745 |
| High-ARB | | − 5.7 ± 7.9 (21) | − 2.6 ± 8.0 (19) | − 3.1 ± 8.0 (20) | 0.1809 | |

(high-AML vs. high-ARB, $p = 0.048$). Serum LDL-C levels were significantly decreased only in the high-AML group: − 10.1 ± 14.70 mg/dL in the high-AML group ($p = 0.011$ vs. week 0) and − 1.3 ± 24.57 mg/dL in the high-ARB group ($p = 0.973$ vs. week 0) (high-AML vs. high-ARB, $p = 0.089$).

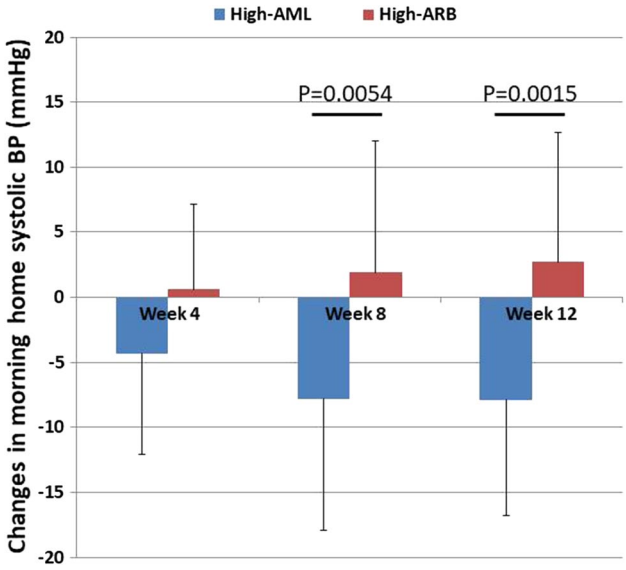


**Fig. 3** Changes in morning home systolic BP (mmHg). BP, blood pressure. The changes in morning home systolic BP from week 0 were evaluated by Mixed-Effect Model Repeated Measure (MMRM) and compared using the Bonferroni correction

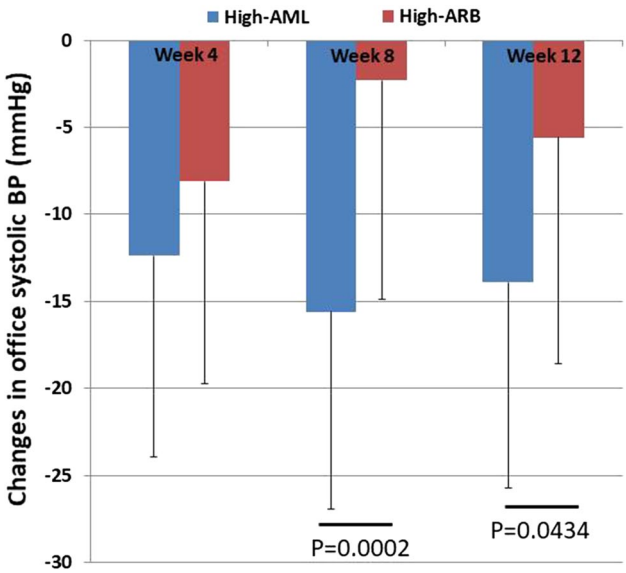


**Fig. 4** Changes in office systolic BP (mmHg). *BP* blood pressure. The changes in morning home systolic BP from week 0 were evaluated by Mixed-Effect Model Repeated Measure (MMRM) and compared using the Bonferroni correction

## Adverse events

There were no serious adverse events related to the treatment in either group. Although several non-serious adverse events related to treatment were noted (edema, erythema and impairment of renal function), there were no significant differences between the groups, and there was also no difference in symptoms potentially related to BP management (data not shown).

## Discussion

This ACADEMIE study shows that increasing the dose of amlodipine, but not ARB, significantly reduced home morning systolic BP in patients with type 2 diabetes who were already receiving combination therapy with medium doses of amlodipine and ARB. Home morning diastolic BP, home systolic and diastolic BP before going to bed, and office systolic BP were also reduced after increasing the dose of amlodipine, but not ARB. Although there were significant differences in home morning systolic BP between the two groups, there were no significant differences in adverse events related to BP management. We also performed a prespecified subgroup analysis and confirmed that for both systolic BP ≥ 140 mmHg and systolic BP < 140 mmHg, home morning systolic BP was significantly lower in the high-AML group than in the high-ARB group ($p = 0.0035$ for systolic BP ≥ 140 mmHg, $p = 0.0309$ for systolic BP < 140 mmHg). Thus, there were no interactions between baseline office systolic BP and the difference between the groups.

It is important, but difficult, to adequately control BP in diabetic patients with hypertension. The important result of this ACADEMIE study is that we identified which drug should be increased to achieve a stronger antihypertensive effect in diabetic patients with hypertension. These results were consistent with the previous ADVANCED-J study, which showed that an amlodipine combination regimen (medium doses of ARB and amlodipine) was superior to an increased ARB regimen (high dose of ARB without amlodipine) in type 2 diabetes patients with hypertension [15]. In that previous study, the reduction of morning home systolic BP was − 15.5 mmHg after amlodipine was added to the medium dose of ARB, and − 2.3 mmHg after an increase in ARB. Although the reductions in morning home systolic BP in both groups in our study were smaller than those in the previous study, i.e., − 7.9 mmHg in the high-AML group and + 2.7 mmHg in the high-ARB group, this was probably because the participants in our study had already been taking medium doses of amlodipine in addition to a medium dose of ARB.

The Systolic BP Intervention Trial (SPRINT) showed that a target systolic BP < 120 mmHg resulted in lower rates of major cardiovascular events and death from any cause compared to a target of < 140 mmHg in non-diabetic participants who were at high risk for cardiovascular events [17].

**Table 3.** Change in biomarkers

| | Week 0<br>Mean ± SD (*n*) | Week 4<br>Mean ± SD (*n*) | Week 12<br>Mean ± SD (*n*) | Week 0 vs. week 12 | CCV vs. ARB |
|---|---|---|---|---|---|
| Urinary albumin (mg/g Cr) | | | | | |
| High-AML | 130.9 ± 229.52 (19) | 121.8 ± 171.47 (20) | 157.4 ± 225.76 (19) | | |
| High-ARB | 446.7 ± 676.97 (20) | 390.5 ± 744.94 (21) | 366.3 ± 525.08 (20) | | |
| Change in urinary albumin | | | | | |
| High-AML | | − 11.5 ± 95.65 (18) | 24.1 ± 163.84 (17) | 0.6318 | 0.8397 |
| High-ARB | | − 40.1 ± 339.54 (20) | 23.3 ± 335.65 (19) | 0.8876 | |
| L-FABP (ug/g Cr) | | | | | |
| High-AML | 5.72 ± 6.197 (16) | 7.16 ± 7.353 (17) | 5.76 ± 6.469 (18) | | |
| High-ARB | 14.64 ± 26.115 (20) | 10.44 ± 15.076 (20) | 17.58 ± 22.325 (19) | | |
| Change in L-FABP | | | | | |
| High-AML | | 0.54 ± 2.165 (15) | 0.53 ± 7.568 (15) | 0.9126 | 0.1606 |
| High-ARB | | − 4.68 ± 19.754 (19) | 2.39 ± 20.248 (18) | 0.7415 | |
| Hs-CRP (mg/dL) | | | | | |
| High-AML | 0.515 ± 1.6613 (20) | 0.292 ± 0.8251 (20) | 0.496 ± 0.9810 (19) | | |
| High-ARB | 0.144 ± 0.1384 (20) | 0.277 ± 0.5377 (21) | 0.197 ± 0.3469 (20) | | |
| Change in hs-CRP | | | | | |
| High-AML | | − 0.195 ± 0.8636 (19) | − 0.011 ± 1.1344 (18) | 0.9993 | 0.6977 |
| High-ARB | | 0.137 ± 0.5534 (20) | 0.063 ± 0.2637 (19) | 0.8042 | |
| Pentraxin 3 (ng/mL) | | | | | |
| High-AML | 1.67 ± 0.531 (20) | 1.67 ± 0.553 (20) | 1.76 ± 0.901 (19) | | |
| High-ARB | 1.94 ± 1.642 (20) | 1.72 ± 0.892 (21) | 1.89 ± 0.982 (20) | | |
| Change in pentraxin 3 | | | | | |
| High-AML | | − 0.03 ± 0.420 (19) | 0.05 ± 0.516 (18) | 0.9045 | 0.7968 |
| High-ARB | | − 0.23 ± 0.900 (20) | − 0.09 ± 0.950 (19) | 0.8763 | |
| Adiponectin (ug/mL) | | | | | |
| High-AML | 9.43 ± 3.637 (20) | 9.88 ± 3.646 (20) | 9.62 ± 4.001 (19) | | |
| High-ARB | 8.23 ± 4.096 (20) | 8.42 ± 4.114 (21) | 8.87 ± 4.661 (20) | | |
| Change in adiponectin | | | | | |
| High-AML | | 0.42 ± 0.700 (19) | 0.37 ± 1.446 (18) | 0.2620 | 0.4044 |
| High-ARB | | 0.10 ± 0.729 (20) | 0.58 ± 1.260 (19) | 0.0257 | |

*L-FABP* L-type fatty acid binding protein, *Hs-CRP* high sensitive C-reactive protein.

In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which investigated whether therapy with a target systolic BP < 120 mmHg reduced major cardiovascular events in patients with type 2 diabetes who were at high risk for cardiovascular events, showed that a lower BP target (< 120 mmHg) was associated with a lower incidence of stroke (hazard ratio, 0.59) [18]. A meta-analysis of 19 trials including 44,989 participants suggested that intensive blood-pressure treatment reduced major cardiovascular events, myocardial infarction, stroke, albuminuria, and retinopathy progression, and these beneficial effects were consistent across patient subgroups including diabetes [19]. Thus, lowering BP in diabetic patients with hypertension should be especially important in addition to the fact that diabetic patients have a 10-year ASCVD risk ≥ 10% [6]. However, the results of the ADVANCED-J study showed that it may be difficult to control hypertension in diabetic patients even with CCB plus a standard dose of ARB in a relatively short period, since the morning home BP achieved with a combination regimen was 142.7/76.3 mmHg at 8 weeks [15]. BP control was also difficult in all of the participants in both groups in our study; i.e., even though all of the participants were already being treated with medium doses of amlodipine and ARB at baseline, BP was higher than recommended in the ACC/AHA guidelines.

The results of a meta-analysis of 29 randomized trials (total number of patients = 162,341) suggested that treatment with any regimen reduces the risk of total major cardiovascular events, and BP reduction was a more important determinant of risk reduction than the choice of antihypertensive drug [20]. However, the results of the present ACADEMIE study showed that the choice

**Table 4.** Change in glucose and lipid profiles.

| | Week 0 | Week 4 | Week 12 | *P* value | |
|---|---|---|---|---|---|
| | Mean ± SD (*n*) | Mean ± SD (*n*) | Mean ± SD (*n*) | week 0 vs. week 12 | CCV vs. ARB |
| Glucose (mg/dL) | | | | | |
| High-AML | 141.4 ± 47.99 (20) | 135.1 ± 41.27 (20) | 142.7 ± 44.17 (19) | | |
| High-ARB | 172.3 ± 82.39 (20) | 162.2 ± 43.18 (21) | 152.8 ± 48.38 (20) | | |
| Change in glucose | | | | | |
| High-AML | | − 5.6 ± 48.88 (19) | 0.6 ± 73.31 (18) | 0.9810 | 0.7465 |
| High-ARB | | − 8.6 ± 62.64 (20) | − 19.8 ± 78.98 (19) | 0.3395 | |
| HbA1c (%) | | | | | |
| High-AML | 6.77 ± 0.660 (20) | 6.74 ± 0.664 (20) | 6.83 ± 0.647 (19) | | |
| High-ARB | 7.16 ± 1.304 (20) | 7.21 ± 1.326 (21) | 7.08 ± 1.156 (20) | | |
| Change in HbA1c (%) | | | | | |
| High-AML | | − 0.03 ± 0.148 (19) | 0.03 ± 0.360 (18) | 0.8347 | 0.0480 |
| High-ARB | | − 0.03 ± 0.227 (20) | − 0.25 ± 0.801 (19) | 0.1755 | |
| Total cholesterol (mg/dL) | | | | | |
| High-AML | 177.4 ± 33.75 (20) | 174.4 ± 35.68 (20) | 170.4 ± 31.57 (19) | | |
| High-ARB | 170.1 ± 30.19 (19) | 164.8 ± 31.09 (20) | 163.9 ± 32.69 (19) | | |
| Change in total cholesterol | | | | | |
| High-AML | | − 0.6 ± 10.27 (19) | − 3.6 ± 15.82 (18) | 0.4003 | 0.9363 |
| High-ARB | | − 4.4 ± 23.07 (19) | − 2.5 ± 22.36 (18) | 0.7823 | |
| Trigryceride (mg/dL) | | | | | |
| High-AML | 160.3 ± 79.73 (20) | 158.0 ± 68.55 (20) | 196.3 ± 148.02 (19) | | |
| High-ARB | 180.8 ± 90.00 (20) | 152.5 ± 64.65 (21) | 168.4 ± 131.77 (20) | | |
| Change in trigryceride | | | | | |
| High-AML | | − 4.1 ± 74.14 (19) | 35.1 ± 124.94 (18) | 0.3200 | 0.1587 |
| High-ARB | | − 25.2 ± 47.35 (20) | − 2.7 ± 115.99 (19) | 0.9818 | |
| HDL-C (mg/dL) | | | | | |
| High-AML | 50.8 ± 13.42 (20) | 50.1 ± 12.01 (20) | 49.1 ± 14.79 (19) | | |
| High-ARB | 48.5 ± 11.62 (20) | 49.1 ± 13.25 (21) | 47.5 ± 11.91 (20) | | |
| Change in HDL-C | | | | | |
| High-AML | | 0.8 ± 5.18 (19) | − 0.3 ± 6.23 (18) | 0.9506 | 0.3926 |
| High-ARB | | 0.4 ± 4.52 (20) | − 1.4 ± 4.45 (19) | 0.3400 | |
| LDL-C (mg/dL) | | | | | |
| High-AML | 94.5 ± 30.31 (20) | 92.7 ± 29.59 (20) | 82.1 ± 33.85 (19) | | |
| High-ARB | 85.1 ± 26.36 (19) | 85.1 ± 27.81 (20) | 82.6 ± 36.76 (19) | | |
| Change in LDL-C | | | | | |
| High-AML | | − 0.1 ± 12.14 (20) | − 10.1 ± 14.70 (19) | 0.0107 | 0.0890 |
| High-ARB | | − 0.4 ± 20.39 (20) | − 1.3 ± 24.57 (19) | 0.9728 | |

The serum LDL-C level was calculated indirectly using the Friedewald formula.

*HbA1c* hemoglobin A1c, *HDL-C* high density lipoprotein cholesterol, *LDL-C* low density lipoprotein cholesterol

of antihypertensive drug is important and related to the degree of BP reduction in diabetic patients with hypertension. The results of the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) study underscore this notion. The VALUE study reported that the most consistent and significant difference between a valsartan-based regimen and an amlodipine-based regimen in hypertensive patients at high cardiovascular risk was BP control [21]. Amlodipine-based therapy was more effective for reducing BP, and this effect was more pronounced during the early phases of the study. In addition, this difference persisted throughout the study period, suggesting that the early control of BP is important for long-lasting BP control. Although the study period in the ACADEMIE study was only 12 weeks, it is reasonable to assume that the differences in BP between the two groups would persist.

Since proteinuria predicts a poor renal outcome in diabetic patients with hypertension, we also studied the effect of the treatment strategy on proteinuria. As a result, there were no significant effects on urinary albumin, cystatin C, or L-FABP. There were also no differences in the inflammatory markers high sensitive CRP and pentraxin 3. Since ARB has been reported to have anti-inflammatory effects [22,23], and to reduce proteinuria and microalbuminuria [24–26], these results were presumably due to the small sample size and short study period, and because all of the participants were already receiving a medium dose of ARB at baseline. Serum adiponectin levels were significantly increased only in the high-ARB group, but the effects of these changes on cardiovascular outcomes are uncertain. Previous reports showed that antihypertensive drugs, and especially RAS blockers, increased adiponectin levels [27]. Furuhashi et al. reported that a low level of adiponectin is related to insulin resistance in hypertension, and RAS blockade with ARB or an ACE inhibitor increased adiponectin levels in patients with essential hypertension [28]. Nomura et al. reported that the plasma adiponectin level was significantly lower in hypertensive patients with diabetes than in those without diabetes. Treatment with the ARB valsartan increased the adiponectin level in patients with type 2 diabetes, but not in those with non-type 2 diabetes [29]. Our study showed that ARBs increase adiponectin levels, consistent with these previous studies. Adiponectin has been shown to affect the insulin-sensitivity of skeletal muscle, and the plasma concentration of adiponectin is inversely correlated with insulin resistance in type 2 diabetic patients [30]. The difference in the change in HbA1c between the two groups may bedue to the increased adiponectin levels in the high-ARB group. In addition, the results of a meta-analysis of prospective, randomized, placebo-controlled or active-controlled trials suggested that inhibition of the renin-angiotensin system could prevent the new onset of diabetes [31].

LDL-C levels were significantly decreased only in the high-AML group, as in previous studies [32,33], but the mechanisms of these changes are unclear.

We used morning BP obtained by home BP monitoring with an automated measurement system as a primary endpoint since it is more useful for the detection of inadequate BP control than clinical BP measurement [11,34]. Ambulatory BP monitoring (ABPM) is better for predicting long-term CVD outcomes than office BP since elevated ABPM has been associated with an increased risk for fatal and non-fatal stroke and cardiovascular events independent of office BP [35]. It has also been reported that elevated home BP is associated with an increased risk for ASCVD and is a strong predictor of ASCVD [35,36].

In this ACADEMIE study, 42 of the original 121 patients were excluded due to the exclusion criteria of BP (systolic BP < 130 mmHg and diastolic BP < 80 mmHg) after the observation period, and thus only 67 eligible participants were randomized into the two groups. There are several possible reasons for this unexpectedly high rate of exclusion. First, there is evidence that participants in a study modify their behavior, which may be lead to improvements in participant performance and affect the result of the study (Hawthorne Effect) [37,38]. Accordingly, mere enrollment in the ACADEMIE study may affected the BP of the participants before any change in the doses of antihypertensive drugs. Second, compared with usual care, the self-monitoring of BP on its own can result in reduced systolic BP and diastolic BP, as reported in a previous study [39]. Our study participants started to self-monitor BP during the observation period before allocation (the study algorithms are shown in Fig. 1). Third, it was reported that the proportion of patients with adequately controlled BP was lower in winter than in summer [13]. Since our study was conducted in both winter and summer, some patients were enrolled in a relatively cold season. When these patients were allocated after the 4-week observation period, it was warmer, which could have caused reduced BP in these patients. Therefore, these changes in BP might be the result of seasonal variation. This seasonal variation may have also affected the BP change after allocation and may have caused an increased BP in the high-ARB group or reduced the reduction in BP in the high-AML group.

This study has several limitations. First, the number of participants was small, especially those who were eventually allocated into the two groups. In addition, the percentage of participants who persisted with continuous home BP measurement was much lower than anticipated. Second, 12 weeks is too short a time to observe cardiovascular benefits from the reduction of BP. Although the results of our study suggest that reduction of morning home BP with an increase in the dose of amlodipine would probably lead to a reduction in cardiovascular events, further studies are warranted. Third, this study had an open-label design, in that the kind of antihypertensive drug that was increased was not masked, which could have potentially caused a bias. However, this was not likely to have affected the measurement of home BP since BP was measured with an automated telemonitoring system.

## Conclusions

In conclusion, this ACADEMIE study evaluated which antihypertensive drug, amlodipine or ARB, should be increased as an add-on therapy to treat patients with type 2 diabetes who do not reach their target BP under combination therapy with medium doses of amlodipine (CCB) and ARB. Our results clearly showed that an increase in the dose of amlodipine is superior to an increase in the dose of ARB for the reduction of home morning systolic BP in patients with type

2 diabetes. To our knowledge, this is the first study to demonstrate which drug should be increased in these patients.

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## Compliance with ethical standards

**Conflict of interest** The ACADEMIE trial was sponsored by Sumitomo Dainippon Pharma Co., Ltd. K.S. is a Chief Director and S.M. is a Director of NPO Clinical and Applied Science, Fukuoka, Japan. K.S. has an Endowed "Department of Molecular Cardiovascular Therapeutics" supported by MSD, Co. LTD. S.M. belongs to the Department of Molecular Cardiovascular Therapeutics, which is supported by MSD, Co. LTD. K.S. and S.M. have received grants and lecture honoraria from Daiichi-Sankyo Co, Takeda Pharm. Co. Ltd., Bayer Yakuhin Pharm., and Astellas Pharma Inc.

## References

1. Adler AI, Stratton IM, Neil HA, Yudkin JS, Matthews DR, Cull CA, Wright AD, Turner RC, Holman RR (2000) Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. BMJ 321:412–419
2. Stamler J, Vaccaro O, Neaton JD, Wentworth D (1993) Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care 16:434–444
3. Chen G, McAlister FA, Walker RL, Hemmelgarn BR, Campbell NR (2011) Cardiovascular outcomes in framingham participants with diabetes: the importance of blood pressure. Hypertension 57:891–897
4. Kannel WB, Wilson PW, Zhang TJ (1991) The epidemiology of impaired glucose tolerance and hypertension. Am Heart J 121:1268–1273
5. Tarnow L, Rossing P, Gall MA, Nielsen FS, Parving HH (1994) Prevalence of arterial hypertension in diabetic patients before and after the JNC-V. Diabetes Care 17:1247–1251
6. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC Jr, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA Sr, Williamson JD, Wright JT Jr (2017) 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. https://doi.org/10.1161/hyp.0000000000000065
7. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F (2014) 2013 ESH/ESC Practice Guidelines for the Management of Arterial Hypertension. Blood Press 23:3–16
8. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, Lackland DT, LeFevre ML, MacKenzie TD, Ogedegbe O, Smith SC Jr, Svetkey LP, Taler SJ, Townsend RR, Wright JT Jr, Narva AS, Ortiz E (2014) 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 311:507–520
9. Palmer SC, Mavridis D, Navarese E, Craig JC, Tonelli M, Salanti G, Wiebe N, Ruospo M, Wheeler DC, Strippoli GF (2015) Comparative efficacy and safety of blood pressure-lowering agents in adults with diabetes and kidney disease: a network meta-analysis. Lancet 385:2047–2056
10. Schmieder RE, Hilgers KF, Schlaich MP, Schmidt BM (2007) Renin-angiotensin system and cardiovascular risk. Lancet 369:1208–1219
11. Krause T, Lovibond K, Caulfield M, McCormack T, Williams B (2011) Management of hypertension: summary of NICE guidance. BMJ 343:d4891
12. Ostergren J, Poulter NR, Sever PS, Dahlof B, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E (2008) The Anglo-Scandinavian Cardiac Outcomes Trial: blood pressure-lowering limb: effects in patients with type II diabetes. J Hypertens 26:2103–2111
13. Mori H, Ukai H, Yamamoto H, Saitou S, Hirao K, Yamauchi M, Umemura S (2006) Current status of antihypertensive prescription and associated blood pressure control in Japan. Hypertens Res 29:143–151
14. Grossman Y, Shlomai G, Grossman E (2014) Treating hypertension in type 2 diabetes. Expert Opin Pharmacother 15:2131–2140
15. Miyauchi K, Yamazaki T, Watada H, Tanaka Y, Kawamori R, Imai Y, Ikeda S, Kitagawa A, Ono Y, Murayama F, Choi JB, Suwa S, Hayashi D, Kishimoto J, Daida H (2012) Management of home blood pressure by amlodipine combined with angiotensin II receptor blocker in type 2 diabetes. Circ J 76:2159–2166
16. Okada T, Tanaka H, Kaisei E, Inoue T, Miyoshi H, Ono H, Kuwahara M,Miyake R (2013) Amlodipine10mg/ARB heiyouryouhou to, amlodipine5mg/ARB heiyouryouhou no kouatsukouka no hikakukentou. J Blood Press 20(11):1131–1137 **(in Japanese)**
17. Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, Reboussin DM, Rahman M, Oparil S, Lewis CE, Kimmel PL, Johnson KC, Goff DC Jr, Fine LJ, Cutler JA, Cushman WC, Cheung AK, Ambrosius WT (2015) A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 373:2103–2116
18. Cushman WC, Evans GW, Byington RP, Goff DC Jr, Grimm RH Jr, Cutler JA, Simons-Morton DG, Basile JN, Corson MA, Probstfield JL, Katz L, Peterson KA, Friedewald WT, Buse JB, Bigger JT, Gerstein HC, Ismail-Beigi F (2010) Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 362:1575–1585
19. Xie X, Atkins E, Lv J, Bennett A, Neal B, Ninomiya T, Woodward M, MacMahon S, Turnbull F, Hillis GS, Chalmers J, Mant J, Salam A, Rahimi K, Perkovic V, Rodgers A (2016) Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. Lancet 387:435–443
20. Turnbull F (2003) Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. Lancet 362:1527–1535
21. Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, Hua T, Laragh J, McInnes GT, Mitchell L, Plat F, Schork A, Smith B, Zanchetti A (2004) Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet 363:2022–2031

22. Morii J, Miura S, Ike A, Shiga Y, Sugihara M, Iwata A, Kawamura A, Nishikawa H, Saku K (2013) Comparison of the efficacies of irbesartan and olmesartan after successful coronary stent implantation. Intern Med 52:713–719
23. Sugihara M, Miura S, Takamiya Y, Kiya Y, Arimura T, Iwata A, Kawamura A, Nishikawa H, Uehara Y, Saku K (2009) Safety and efficacy of antihypertensive therapy with add-on angiotensin II type 1 receptor blocker after successful coronary stent implantation. Hypertens Res 32:625–630
24. Haller H, Ito S, Izzo JL Jr, Januszewicz A, Katayama S, Menne J, Mimran A, Rabelink TJ, Ritz E, Ruilope LM, Rump LC, Viberti G (2011) Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. N Engl J Med 364:907–917
25. Xu R, Sun S, Huo Y, Yun L, Huang S, Li G, Yan S (2015) Effects of ACEIs versus ARBs on proteinuria or albuminuria in primary hypertension: a meta-analysis of randomized trials. Medicine (Baltimore) 94:e1560
26. Parving HH, Lehnert H, Brochner-Mortensen J, Gomis R, Andersen S, Arner P (2001) The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med 345:870–878
27. Karthikeyan VJ, Lip GY (2007) Antihypertensive treatment, adiponectin and cardiovascular risk. J Hum Hypertens 21:8–11
28. Furuhashi M, Ura N, Higashiura K, Murakami H, Tanaka M, Moniwa N, Yoshida D, Shimamoto K (2003) Blockade of the renin-angiotensin system increases adiponectin concentrations in patients with essential hypertension. Hypertension 42:76–81
29. Nomura S, Shouzu A, Omoto S, Nishikawa M, Fukuhara S, Iwasaka T (2006) Effect of valsartan on monocyte/endothelial cell activation markers and adiponectin in hypertensive patients with type 2 diabetes mellitus. Thromb Res 117:385–392
30. Nicholson T, Church C, Baker DJ, Jones SW (2018) The role of adipokines in skeletal muscle inflammation and insulin sensitivity. J Inflamm (Lond) 15:9
31. Andraws R, Brown DL (2007) Effect of inhibition of the renin-angiotensin system on development of type 2 diabetes mellitus (meta-analysis of randomized trials). Am J Cardiol 99:1006–1012
32. Arslan Z, Ay SA, Karaman M, Cakar M, Celik T, Balta S, Akhan M, Sarlak H, Arslan E, Demirbas S, Demirkol S, Bulucu F, Saglam K (2013) An additional LDL-lowering effect of amlodipine; not only an antihypertensive? Clin Exp Hypertens 35:449–453
33. Lender D, Arauz-Pacheco C, Breen L, Mora-Mora P, Ramirez LC, Raskin P (1999) A double blind comparison of the effects of amlodipine and enalapril on insulin sensitivity in hypertensive patients. Am J Hypertens 12:298–303
34. Park SJ, Park JB, Choi DJ, Youn HJ, Park CG, Ahn YK, Shin JH, Kim DW, Rim SJ, Bae JH, Park HY (2011) Detection of masked hypertension and the 'mask effect' in patients with well-controlled office blood pressure. Circ J 75:357–365
35. Siu AL (2015) Screening for high blood pressure in adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 163:778–786
36. Niiranen TJ, Hanninen MR, Johansson J, Reunanen A, Jula AM (2010) Home-measured blood pressure is a stronger predictor of cardiovascular risk than office blood pressure: the Finn-Home study. Hypertension 55:1346–1351
37. McCarney R, Warner J, Iliffe S, van Haselen R, Griffin M, Fisher P (2007) The Hawthorne effect: a randomised, controlled trial. BMC Med Res Methodol 7:30
38. Fox NS, Brennan JS, Chasen ST (2008) Clinical estimation of fetal weight and the Hawthorne effect. Eur J Obstet Gynecol Reprod Biol 141:111–114
39. Uhlig K, Balk EM, Patel K, Ip S, Kitsios GD, Obadan NO, Haynes SM, Stefan M, Rao M Kong Win Chang L, Gaylor J Iovin RC (2012) Self-Measured Blood Pressure Monitoring: Comparative Effectiveness. Agency for Healthcare Research and Quality (US) Report No.: 12-EHC002-EF.