Effects of triple combination therapy with azilsartan/amlodipine/hydrochlorothiazide on office/home blood pressure: a randomized-controlled trial in Japanese essential hypertensive patients

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Objective **The efficacy and safety of triple therapy with azilsartan (AZI), amlodipine besylate (AML), and hydrochlorothiazide (HCTZ) compared with dual therapy with AZI/AML or HCTZ monotherapy were evaluated in Japanese essential hypertensive patients in a double-blinded manner.**

Patients and methods **A total of 353 patients with office blood pressure (BP) of at least 150/95 mmHg were randomized to a 10-week treatment with AZI/AML/HCTZ 20/5/12.5 mg, AZI/AML/HCTZ 20/5/6.25 mg, AZI/AML 20/5 mg, HCTZ 12.5 mg, or HCTZ 6.25 mg.**

Results **The mean change from baseline in office diastolic/systolic BPs at week 10 was −25.9/−41.4, −24.9/−38.6, and −22.4/−34.5 mmHg in the AZI/AML/HCTZ 20/5/12.5 mg, AZI/AML/HCTZ 20/5/6.25 mg, and AZI/AML 20/5 mg groups, respectively. AZI/AML/HCTZ 20/5/12.5 mg led to a significantly greater reduction in diastolic and systolic BP than the dual therapy. In addition, the change in home diastolic BP measured with telemetry devices showed a significant difference between the two triple therapy groups. The incidences of adverse events except dizziness postural were similar among the treatment groups in the triple therapy groups.**

Conclusion **Triple therapy with AZI/AML/HCTZ 20/5/12.5 mg shows a greater antihypertensive effect than the dual therapy and has acceptable safety profiles for Japanese essential hypertensive patients. It was also observed that home BP measurement by automated telemetry could detect changes in BP that were not detected in office BP measurement, although further investigation is needed.** ***Blood Press Monit*** **00:000–000**

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Keywords: amlodipine, azilsartan, blood pressure, hydrochlorothiazide, randomized-controlled trial, triple combination therapy

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Introduction

The Japanese Society of Hypertension (JSH) Guidelines for the Management of Hypertension (JSH 2014) recommend triple combination therapy of an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker (ARB) with calcium channel blockers (CCBs) and a diuretic in patients whose blood pressure (BP) cannot be controlled adequately with dual combination therapy. It is also recommended to add a low-dose diuretic as a third drug if dual therapy excludes a diuretic [1]. Azilsartan (AZI) is an ARB that has been approved for the treatment of hypertension in Japan. A previous study showed that AZI (20–40 mg once daily) led to a significantly greater reduction both in seated trough diastolic blood pressure (DBP) and in seated trough systolic blood pressure (SBP) than candesartan cilexetil (8–12 mg once daily) in Japanese patients with grade I–II essential hypertension [2]. Amlodipine besylate (AML) is a long-acting CCB designed to correct the defects of dihydropyridine CCBs such as reflex sympathetic stimulation [3]. The safety and efficacy of AML have been well established [4], and thus, it is the most widely used CCB in Japan. Hydrochlorothiazide (HCTZ) is a thiazide diuretic that exerts an antihypertensive effect by decreasing sodium chloride reabsorption at different sites in the nephron, thus increasing the urinary excretion of sodium chloride and water loss [5]. When HCTZ is used in combination with an ARB, the two drugs are expected to balance out each other's side effects [6].

We have reported previously that the BP-lowering effect of the dual combination of AZI and AML is greater than that of monotherapy with either of these drugs, and the safety and tolerability of this combination are comparable

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with that of each component [7]. Recently, other studies have reported that HCTZ exerted an additive antihypertensive effect when used in combination with an ARB and AML [8,9]. Thus, the combination of AZI, AML, and HCTZ appears to be a rational choice on the basis of the complementary mechanisms of action of these drugs.

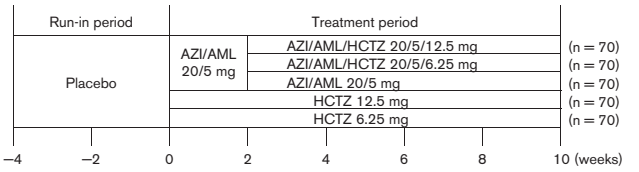
The primary objective of the current study was to evaluate the efficacy and safety of AZI/AML/HCTZ (20/5/12.5 mg and 20/5/6.25 mg) triple therapy in Japanese essential hypertensive patients by comparing these two combinations of triple therapy with AZL/AML dual therapy, and the secondary objective was to compare the safety of AZL/AML/HCTZ triple therapy with that of HCTZ monotherapy. In this study, the doses of AZI and AML were set as 20 and 5 mg, respectively, because these doses are most commonly used in Japan. As for HCTZ, although the approved dose is 25 mg in Japan, the treatment guideline JSH 2014 recommends the use of low-dose diuretics (1/4–1/2 of the approved dose) to reduce adverse drug reactions. Thus, the doses of HCTZ were set as 6.25 and 12.5 mg in this study. Home blood pressure (HBP) monitoring by automated telemetry was also performed as an exploratory endpoint to address its importance in the treatment of hypertension.

Patients and methods

Study design

This study was a multicenter, randomized, double-blind, parallel-group study in Japan, and consisted of a 4-week single-blind placebo run-in period and a 10-week treatment period. Patients visited the medical centers at weeks −4, −2, 0, 2, 4, 6, 8, and 10. All antihypertensive drugs were stopped before starting the study, and all patients underwent a 4-week wash-out placebo period. At week 0, eligible patients were assigned randomly at a ratio of 1 : 1 : 1 : 1 : 1 to one of the following five treatment groups: the AZI/AML/HCTZ 20/5/12.5 mg or 20/5/6.25 mg triple therapy group, the AZI/AML 20/5 mg dual therapy group, or the HCTZ 12.5 or 6.25 mg monotherapy group. To avoid the development of hypotension when treatment started, patients assigned to the triple therapy groups were treated with AZI/AML 20/5 mg for 2 weeks, followed by the triple therapy for 8 weeks, with the use of forced titration. Other patients were treated by their assigned treatments for 10 weeks (Fig. 1). Patients received the study drugs in a blinded manner once daily in the morning at a fixed time either in a fasting or a fed state. A tablet containing AZL/AML 20/5 mg, a tablet containing HCTZ 6.25 mg, and both of these placebo tablets were used. Each patient took three tablets/day: one active or placebo AZI/AML tablet and two tablets of one of the various combinations of the active and placebo HCTZ tablets. Throughout the study, the concomitant use of other antihypertensive drugs was not allowed.

Fig. 1



Study design overview. AML, amlodipine besilate; AZI, azilsartan; HCTZ, hydrochlorothiazide.

Study population

Patients were eligible for study participation if they fulfilled all of the following main inclusion criteria: essential hypertension with an office seated systolic blood pressure (OSBP) of at least 150 and less than 180 mmHg and an office seated diastolic blood pressure (ODBP) of at least 95 and less than 110 mmHg at weeks −2 and 0 of the placebo run-in period, age 20 years or older, and being able to comprehend and sign the informed consent form. Patients were not eligible for study participation if they fulfilled any of the following main exclusion criteria: diagnoses of secondary or grade III hypertension, severe cardiovascular diseases such as myocardial infarction (within 24 weeks before the start of the placebo run-in period), coronary arterial revascularization (within 24 weeks before the start of the placebo run-in period), severe valvular diseases, atrial fibrillation, or the following diseases that require medication: angina pectoris, congested heart failure, or arrhythmia, severe liver dysfunction (e.g. aspartate aminotransferase or alanine aminotransferase levels ≥ 2.5 times the upper limit of normal at week −2 in the placebo run-in period), severe renal dysfunctions (e.g. serum creatinine level ≥ 2.0 times the upper limit of normal at week −2 in the placebo run-in period), hyperkalemia (e.g. serum K level ≥ 5.5 mEq/l at a clinical laboratory test at week −2), or malignant tumors. Evident white-coat hypertension or white-coat phenomena were excluded.

This study was approved by the Institutional Review Board at each study site, and was carried out in accordance with the ethical principles of the Declaration of Helsinki, the International Conference on Harmonisation E6 (R1) Guidelines for Good Clinical Practice, and all applicable local laws and regulations. All patients were required to provide written informed consent before the initiation of any study-related procedures. The trial registration of the current study can be found at ClinicalTrials.gov Identifier: NCT02072330; and JAPIC Clinical Trials Information Number: JapicCTI-121962.

Office blood pressure

Office blood pressure (OBP) was measured at least three times at 1- to 2-min intervals after the participant had been sitting for at least 5 min at every visit. Measurements were repeated until two consecutive stable measurements (a difference between the two consecutive measurements < 5

mmHg for sitting DBP or <10 mmHg for sitting SBP) were obtained. The average of the last two consecutive measurements was used for analysis. On the morning of the OBP measurement, patients were not allowed to take the study drug so that OBP was measured in the morning, ~24 h after the last drug intake (acceptable range ± 3 h, i.e. from 21 to 27 h after the last drug intake). Patients were prohibited from consuming caffeine-containing foods/drinks or smoking within 30 min before the OBP measurement. Time points for the evaluation of OBP were set at weeks 0 (baseline), 2, 4, 6, 8, 10, and 10 [last observation carried forward (LOCF)]. OBP was measured using an automated sphygmomanometer (Omron HEM-907; OMRON Healthcare Co. Ltd, Kyoto, Japan) [10] or a mercury sphygmomanometer, which was well validated by vendors. The investigators prepared and used cuffs according to the arm size of each patient so that BP could be measured appropriately. The patients used the same cuff throughout the study. All observers were trained for the procedures by the sponsor before starting measurement.

Home blood pressure

HBP was measured using the MedicalLINK BP-monitoring service system using an automated HBP monitor with telemetry (Omron HEM-7251G; OMRON Healthcare Co. Ltd) [11] with a cuff [Omron HEMCUFF-R22 (measurable range: 170–320mm); OMRON Healthcare Co. Ltd]. Patients received oral and written instructions to obtain HBP measurements three times after 1–2 min of rest in a sitting position each in the morning and evening every day from the evening of the day of the week − 2 visit until the morning of the day of the final visit. Morning BP was measured within 1 h after waking up, between 4 : 00 and 9 : 00, after urinating, but before taking their dose of antihypertensive agents, as well as before breakfast. Evening BP was measured between 19 : 00 and 2 : 00 the next day, and before bedtime. Daily HBP values in the morning and the evening were defined as the average of values that fulfilled all of the following criteria: home diastolic blood pressure (HDBP) of at least 40 and less than or equal to 150 mmHg, home systolic blood pressure (HSBP) of at least 70 and less than or equal to 250 mmHg, and difference between HSBP and HDBP of 10 mmHg or more. Time points for the evaluation of HBP were set at weeks 0 (baseline), 2, 4, 6, 8, 10, and the end of treatment. Except for morning HBP at the end of treatment, morning HBP was calculated as the mean of the daily HBP values in the morning obtained for the last 7 days before each time-point. Morning HBP at the end of treatment was calculated with the morning HBP obtained on the previous 7 days before the final dosing. If the morning HBP values could not be obtained on 4 or more of the 7 days, the morning HBP at that time-point was not calculated.

Safety assessment

Vital signs and physical findings were monitored at every visit, and the severity of adverse events (AEs) and their relationship with the study drugs were assessed by the investigator. Clinical laboratory tests (hematology, serum chemistry, and urinalysis) were measured at weeks − 2, 0 (baseline), 2, 4, 6, 8, and 10 after the patients had fasted for at least 8 h. These measurement tests were performed by Bio Medical Laboratories (BML) Inc. (Tokyo, Japan).

Study endpoints

The efficacy endpoints were the mean change from week 0 (baseline) in the ODBP at week 10 (LOCF) (primary endpoint) and the mean change from week 0 (baseline) in the OSBP at week 10 (LOCF), the mean changes from week 0 (baseline) in the ODBP and OSBP at each time-point, and the proportions of patients who achieved the target OBP (ODBP of <90 mmHg and OSBP of <140 mmHg) at week 10 (LOCF) (secondary endpoints). As an exploratory endpoint, HBP and the proportion of patients who achieved the target HBP (HDBP of <85 mmHg and HSBP of <135 mmHg) were assessed.

Safety endpoints included AEs, vital signs (supine and standing BP, and seated pulse rate), weight, resting 12-lead ECG results, and clinical laboratory tests (hematology, serum chemistry, and urinalysis).

Statistical analysis

Assuming the difference between the AZI/AML/HCTZ 20/5/12.5 mg group and the AZI/AML 20/5 mg group in the mean change from baseline in the ODBP at week 10 (LOCF) to be − 5.0 mmHg, with a common SD of 10.0 mmHg across the treatment groups, 64 patients per group were required to ensure a statistical power of 80% if a two-sample *t*-test with a two-sided significance level of 5% was adopted. Taking patients without available data for the primary endpoint evaluation into account, it was planned to recruit a total of 350 patients (70 patients per group).

The efficacy endpoints were assessed using the full analysis set, which was defined as all patients who were randomized and received at least one dose of the study drug for the treatment period.

For the primary endpoint, the mean change from baseline in the ODBP at week 10 (LOCF) and SD were calculated for each treatment group. The AZI/AML/HCTZ 20/5/12.5 mg group or the AZI/AML/HCTZ 20/5/6.25 mg group was compared with the AZI/AML 20/5 mg group on the basis of the closed testing procedure using 1-way analysis of variance. More specifically, pairwise comparison of the AZI/AML/HCTZ 20/5/12.5 mg group and the AZI/AML 20/5 mg group was performed using a contrast test, and if the result was significant, a pairwise comparison of the AZI/AML/HCTZ 20/5/6.25 mg group and the AZI/AML 20/5 mg group was performed. If the above procedures were followed, a contrast test of the AZI/AML/HCTZ 20/5/6.25 mg group and the AZI/AML 20/5 mg group did not have to be performed in case the

result of comparison of the AZI/AML/HCTZ 20/5/12.5 mg group and the AZI/AML 20/5 mg group was not significant.

For the secondary endpoints, the same analysis as that carried out on the primary endpoint was carried out on OSBP. The proportions of patients who achieved the target OBP were summarized as a secondary endpoints. Comparisons of these proportions between the AZI/AML/HCTZ 20/5/12.5 mg or the AZI/AML/HCTZ 20/5/6.25 mg group and the AZI/AML 20/5 mg group, between the triple therapy groups and their corresponding HCTZ monotherapy groups, and between the AZI/AML/HCTZ 20/5/12.5 mg and the AZI/AML/HCTZ 20/5/6.25 mg groups, were performed using Pearson's χ^2-test.

HBP was analyzed as an exploratory endpoint. The mean change from baseline in HBP at the end of treatment and SD were calculated for each treatment group. The post-hoc comparisons between the AZI/AML/HCTZ 20/5/12.5 mg or the AZI/AML/HCTZ 20/5/6.25 mg group and the AZI/AML 20/5 mg group, between the triple therapy groups and their corresponding HCTZ monotherapy groups, and between the AZI/AML/HCTZ 20/5/12.5 mg and the AZI/AML/HCTZ 20/5/6.25 mg groups were performed by a contrast test using an analysis of covariance model with baseline HBP as a covariate and the treatment group as a factor. The proportions of patients who achieved the target HBP were summarized as an exploratory endpoint. Comparison of these proportions between the groups was performed using the same OBP method as the post-hoc analysis.

Safety endpoints were assessed using the safety analysis set, which was defined as all patients who received at least one dose of the study drug.

For all statistical tests, the significance level was set at 0.05 (two sided).

Results

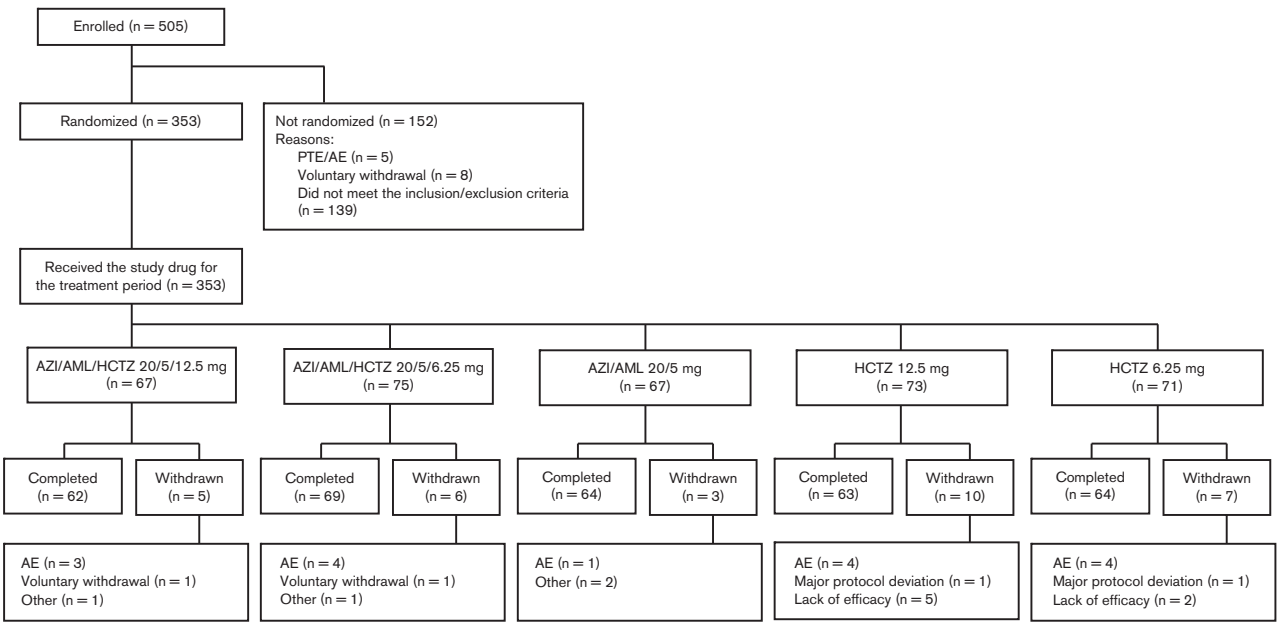
Patient disposition and baseline characteristics

As summarized in Fig. 2, a total of 505 patients provided informed consent. Of these, 353 patients were allocated randomly to the study treatments and received the study drug during the treatment period. The most common primary reason for allocation failure was 'did not meet the inclusion/exclusion criteria' in 139 patients. A total of 67 patients received AZI/AML/HCTZ 20/5/12.5 mg, 75 patients received AZI/AML/HCTZ 20/5/6.25 mg, 67 patients received AZI/AML 20/5 mg, 73 patients received HCTZ 12.5 mg, and 71 patients received HCTZ 6.25 mg. Of these 353 patients, 322 completed the study treatment and 31 withdrew prematurely.

The baseline demographic and clinical characteristics of the randomized patients are summarized in Table 1 and Supplementary Table (Supplemental digital content 1, *http://links.lww.com/BPMJ/A52*).

The mean age of the patients ranged from 56.5 to 58.9 years across all treatment groups. The proportion of male patients ranged from 62.0 to 71.6% across all

Fig. 2



Flow diagram of the enrolled patients. AE, adverse event; AML, amlodipine besilate; AZI, azilsartan; HCTZ, hydrochlorothiazide; PTE, pretreatment event.

treatment groups. The baseline mean ODBP and OSBP ranged from 99.2 to 100.3 mmHg and 159.4 to 162.3 mmHg, respectively, across all treatment groups. Baseline HBP at the morning measurements was available for 347 patients. The baseline mean HDBP and HSBP at the morning measurement ranged from 97.3 to 100.7 mmHg and 153.0 to 157.9 mmHg, respectively, across all treatment groups. The mean HDBP and HSBP values were lower than the mean ODBP and OSBP values in all treatment groups, except the HDBP and ODBP in the AZI/AML/HCTZ 20/5/6.25 mg group. No marked differences in the demographic characteristics were observed among the treatment groups.

Effects of treatment on office blood pressure

Summary statistics of the change from baseline in the OBP at week 10 (LOCF) and the results of the contrast tests are shown in Table 2.

In this study, the changes in the ODBP and OSBP at week 10 (LOCF) were evaluated as the primary and secondary endpoints, respectively. The mean change in the ODBP at week 10 (LOCF) was − 25.9 mmHg in the AZI/AML/HCTZ 20/5/12.5 mg group, − 24.9 mmHg in the AZI/AML/HCTZ 20/5/6.25 mg group, − 22.4 mmHg in the AZI/AML 20/5 mg group, − 8.0 mmHg in the HCTZ 12.5 mg group, and − 8.8 mmHg in the HCTZ 6.25 mg group. The results of the contrast tests in ODBP reduction at week 10 (LOCF) confirmed the superiority of the AZI/AML/HCTZ 20/5/12.5 mg group to the AZI/AML 20/5 mg group ($P = 0.0304$), whereas there was no statistically significant difference between the AZI/AML/HCTZ 20/5/6.25 mg group and the AZI/AML 20/5 mg group ($P = 0.1125$). There was no statistically significant difference between the two triple therapy groups ($P = 0.5253$). The results of comparison of the two triple therapy groups with their corresponding HCTZ monotherapy groups were significant (both $P < 0.0001$).

The mean change in the OSBP at week 10 (LOCF) was − 41.4 mmHg in the AZI/AML/HCTZ 20/5/12.5 mg group, − 38.6 mmHg in the AZI/AML/HCTZ 20/5/6.25 mg group, − 34.5 mmHg in the AZI/AML 20/5 mg group, − 12.5 mmHg in the HCTZ 12.5 mg group, and − 14.6 mmHg in the HCTZ 6.25 mg group. The results of the contrast tests in OSBP reduction at week 10 (LOCF) showed significant differences between the AZI/AML/HCTZ 20/5/12.5 mg group and the AZI/AML 20/5 mg group ($P = 0.0042$), and between the two triple therapy groups and their corresponding HCTZ monotherapy groups (both $P < 0.0001$). However, there were no statistically significant differences between the AZI/AML/HCTZ 20/5/6.25 mg group and the AZI/AML 20/5 mg group ($P = 0.0817$), and between the two triple therapy groups ($P = 0.2275$).

Time profiles of the mean plots of the OBP at each timepoint for each treatment group are shown in Fig. 3.

Table 1 Baseline demographics and characteristics of the study patients (randomized patients)

	Triple therapy		Dual therapy	HCTZ monotherapy		
	AZI/AML/HCTZ 20/5/12.5 mg ($n = 67$)	AZI/AML/HCTZ 20/5/6.25 mg ($n = 75$)	AZI/AML 20/5 mg ($n = 67$)	HCTZ 12.5 mg ($n = 73$)	HCTZ 6.25 mg ($n = 71$)	Total ($n = 353$)
Age [mean (SD)] (years)	56.5 (9.21)	56.9 (9.53)	57.0 (9.85)	58.9 (8.84)	58.8 (8.69)	57.6 (9.23)
Male [*n* (%)]	44 (65.7)	47 (62.7)	48 (71.6)	50 (68.5)	44 (62.0)	233 (66.0)
BMI [mean (SD)] (kg/m^2)	26.16 (3.616)	25.56 (3.851)	25.18 (3.538)	25.64 (3.762)	25.29 (3.162)	25.56 (3.593)
ODBP [mean (SD)] (mmHg)	100.2 (4.17)	99.8 (4.55)	99.5 (4.17)	100.3 (4.19)	99.2 (3.80)	99.8 (4.18)
OSBP [mean (SD)] (mmHg)	160.2 (8.55)	160.3 (7.57)	159.4 (7.27)	162.3 (9.30)	161.9 (8.03)	160.8 (8.21)
HDBP [mean (SD)] (mmHg)	99.3 (9.45)[a]	100.7 (9.60)[b]	97.3 (10.03)	99.1 (9.62)	98.3 (9.27)[c]	99.0 (9.61)[d]
HSBP [mean (SD)] (mmHg)	154.4 (12.48)[a]	156.9 (10.65)[b]	153.0 (14.50)	157.9 (15.15)	157.3 (14.20)[c]	156.0 (13.54)[d]

AML, amlodipine besilate; AZI, azilsartan; HCTZ, hydrochlorothiazide; HDBP, home diastolic blood pressure; HSBP, home systolic blood pressure; ODBP, office diastolic blood pressure; OSBP, office systolic blood pressure.
[a]$n = 64$.
[b]$n = 74$.
[c]$n = 69$.
[d]$n = 347$.

Table 2 Changes from baseline in office trough seated blood pressure at week 10 (last observation carried forward), and home morning and evening blood pressures at the end of treatment (full analysis set)

	Triple therapy		Dual therapy	HCTZ monotherapy	
	AZI/AML/HCTZ 20/5/ 12.5 mg	AZI/AML/HCTZ 20/5/ 6.25 mg	AZI/AML 20/5 mg	HCTZ 12.5 mg	HCTZ 6.25 mg
Change from baseline at week 10 (LOCF) in office trough seated BP					
n	67	74	67	73	71
DBP [mean (SD)] (mmHg)	−25.9 (9.35)	−24.9 (9.82)	−22.4 (8.20)	−8.0 (9.84)	−8.8 (8.68)
Differences in LS means of the triple therapy groups to the dual therapy group					
Point estimate	−3.5	−2.5	–	–	–
95% CI	−6.60 to −0.33	−5.53 to −0.58	–	–	–
P-value	0.0304	0.1125	–	–	–
Differences in LS means of the triple therapy groups to their corresponding HCTZ monotherapy groups					
Point estimate	−17.9	−16.1	–	–	–
95% CI	−20.95 to −14.81	−19.13 to −13.10	–	–	–
P-value	<0.0001	<0.0001	–	–	–
Differences in LS means between the triple therapy groups					
Point estimate	−1.0	–	–	–	–
95% CI	−4.05 to −2.07	–	–	–	–
P-value	0.5253	–	–	–	–
SBP [mean (SD)] (mmHg)	−41.4 (14.62)	−38.6 (14.47)	−34.5 (12.09)	−12.5 (14.73)	−14.6 (12.15)
Differences in LS means of the triple therapy groups to the dual therapy group					
Point estimate	−6.8	−4.0	–	–	–
95% CI	−11.47 to −2.17	−8.57 to −0.51	–	–	–
P-value	0.0042	0.0817	–	–	–
Differences in LS means of the triple therapy groups to their corresponding HCTZ monotherapy groups					
Point estimate	−28.9	−24.0	–	–	–
95% CI	−33.42 to −24.31	−28.45 to −19.50	–	–	–
P-value	<0.0001	<0.0001	–	–	–
Differences in LS means between the triple therapy groups					
Point estimate	−2.8	–	–	–	–
95% CI	−7.33 to −1.75	–	–	–	–
P-value	0.2275	–	–	–	–
Change from baseline at the end of treatment in home morning BP					
n	64	73	65	72	68
DBP [mean (SD)] (mmHg)	−20.5 (7.52)	−18.0 (7.36)	−14.8 (6.53)	−3.8 (6.78)	−2.9 (5.75)
Differences in LS means of the triple therapy groups to the dual therapy group					
Point estimate	−5.3	−2.5	–	–	–
95% CI	−7.56 to −3.09	−4.66 to −0.32	–	–	–
P-value	<0.0001	0.0245	–	–	–
Differences in LS means of the triple therapy groups to their corresponding HCTZ monotherapy groups					
Point estimate	−16.6	−14.5	–	–	–
95% CI	−18.75 to −14.40	−16.65 to −12.37	–	–	–
P-value	<0.0001	<0.0001	–	–	–
Differences in LS means between the triple therapy groups					
Point estimate	−2.8	–	–	–	–
95% CI	−5.00 to −0.66	–	–	–	–
P-value	0.0106	–	–	–	–

SBP [mean (SD)] (mmHg)	−32.7 (10.23)	−30.5 (11.30)	−24.3 (11.40)	−7.9 (9.71)	−5.7 (9.79)
Differences in LS means of the triple therapy groups to the dual therapy group					
Point estimate	−8.2	−5.4	–	–	–
95% CI	−11.61 to −4.70	−8.71 to −2.01	–	–	–
P-value	< 0.0001	0.0018	–	–	–
Differences in LS means of the triple therapy groups to their corresponding HCTZ monotherapy groups					
Point estimate	−25.7	−24.9	–	–	–
95% CI	−29.04 to −22.27	−28.24 to −21.63	–	–	–
P-value	< 0.0001	< 0.0001	–	–	–
Differences in LS means between the triple therapy groups					
Point estimate	−2.8	–	–	–	–
95% CI	−6.16 to −0.57	–	–	–	–
P-value	0.1032	–	–	–	–
Change from baseline at the end of treatment in home evening BP					
n	63	70	60	67	65
DBP [mean (SD)] (mmHg)	−22.0 (8.50)	−19.5 (7.01)	−14.6 (7.05)	−3.2 (7.56)	−3.4 (6.81)
Differences in LS means of the triple therapy groups to the dual therapy group					
Point estimate	−6.5	−4.2	–	–	–
95% CI	−8.95 to −4.10	−6.54 to −1.80	–	–	–
P-value	< 0.0001	0.0006	–	–	–
Differences in LS means of the triple therapy groups to their corresponding HCTZ monotherapy groups					
Point estimate	−18.1	−17.9	–	–	–
95% CI	−20.47 to −15.75	−20.31 to −15.56	–	–	–
P-value	< 0.0001	< 0.0001	–	–	–
Differences in LS means between the triple therapy groups					
Point estimate	−2.4	–	–	–	–
95% CI	−4.69 to −0.03	–	–	–	–
P-value	0.0475	–	–	–	–
SBP [mean (SD)] (mmHg)	−33.0 (11.36)	−31.7 (11.78)	−23.6 (11.08)	−6.7 (10.71)	−5.7 (10.43)
Differences in LS means of the triple therapy groups to the dual therapy group					
Point estimate	−9.1	−7.9	–	–	–
95% CI	−12.69 to −5.53	−11.38 to −4.40	–	–	–
P-value	< 0.0001	< 0.0001	–	–	–
Differences in LS means of the triple therapy groups to their corresponding HCTZ monotherapy groups					
Point estimate	−26.7	−27.6	–	–	–
95% CI	−30.23 to −23.26	−31.10 to −24.08	–	–	–
P-value	< 0.0001	< 0.0001	–	–	–
Differences in LS means between the triple therapy groups					
Point estimate	−1.2	–	–	–	–
95% CI	−4.67 to −2.22	–	–	–	–
P-value	0.4861	–	–	–	–

AML, amlodipine besilate; AZI, azilsartan; BP, blood pressure; CI, confidence interval; DBP, diastolic blood pressure; HCTZ, hydrochlorothiazide; LOCF, last observation carried forward; LS, least square; SBP, systolic blood pressure.

After 12.5 or 6.25 mg of HCTZ was added to AZI/AML 20/5 mg from week 2, further reductions were observed in OBP in both triple therapy groups at week 4 and the reduction was maintained up to week 10.

The proportion of patients who achieved the target OBP (ODBP of <90 mmHg and OSBP of <140 mmHg) at week 10 (LOCF) is shown in Table 3.

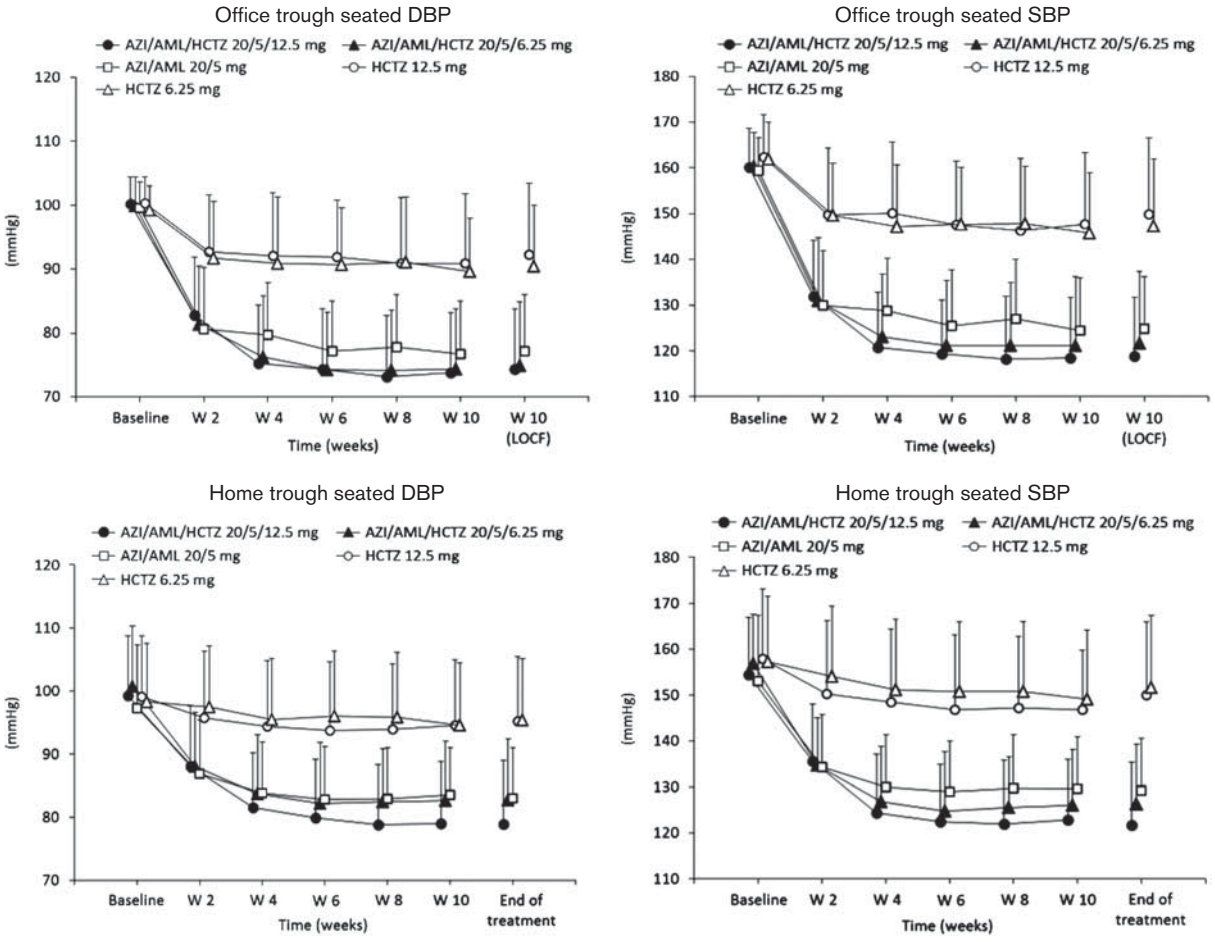
At week 10 (LOCF), the proportion of patients who achieved the target OBP was 92.5% (62/67 patients) in the AZI/AML/HCTZ 20/5/12.5 mg group, 86.5% (64/74 patients) in the AZI/AML/HCTZ 20/5/6.25 mg group, and 83.6% (56/67 patients) in the AZI/AML 20/5 mg group. No significant differences were observed between each triple therapy group and the AZI/AML 20/5 mg group, whereas a significant difference was observed between the triple therapy groups and their corresponding HCTZ monotherapy groups.

Effects of treatment on home blood pressure

Summary statistics of the change from baseline in the HBP in the morning and evening at the end of treatment and the results of the contrast tests are shown in Table 2.

The results were consistent with those obtained for OBP; that is, the results of the contrast tests in the morning HDBP and HSBP reductions at the end of treatment confirmed the superiority of the AZI/AML/HCTZ 20/5/12.5 mg group to the AZI/AML 20/5 mg group ($P < 0.0001$), and of the two triple therapy groups to their corresponding HCTZ monotherapy groups (both $P < 0.0001$). In addition, the mean change from baseline in the HDBP and HSBP at the end of treatment was significantly greater in the AZI/AML/HCTZ 20/5/6.25 mg group than the AZI/AML 20/5 mg group ($P = 0.0245$ and 0.0018, respectively), and a significant difference was observed between the two triple therapy groups in the HDBP ($P = 0.0106$). A similar trend was observed when HBP in the evening was measured.

Fig. 3



Time profiles of the mean plots of the office trough seated DBP and SBP, and home trough seated DBP and SBP at each point. AML, amlodipine besilate; AZI, azilsartan; DBP, diastolic blood pressure; HCTZ, hydrochlorothiazide; LOCF, last observation carried forward; SBP, systolic blood pressure; W, week.

Table 3 Proportion of patients who achieved the target office blood pressure at week 10 (last observation carried forward), or home morning and evening blood pressures at the end of treatment (full analysis set)

	Triple therapy		Dual therapy	HCTZ monotherapy	
	AZI/AML/HCTZ 20/5/12.5 mg	AZI/AML/HCTZ 20/5/6.25 mg	AZI/AML 20/5 mg	HCTZ 12.5 mg	HCTZ 6.25 mg
Office trough seated BP at week 10 (LOCF)					
n	67	74	67	73	71
Patients who achieved the target BP [*n* (%)][a]	62 (92.5)	64 (86.5)	56 (83.6)	15 (20.5)	18 (25.4)
Differences in the proportion of the triple therapy groups to the dual therapy group					
P-value	0.1099	0.6286	–	–	–
Differences in the proportion of the triple therapy groups to their corresponding HCTZ monotherapy groups					
P-value	< 0.0001	< 0.0001	–	–	–
Differences in the proportion between the triple therapy groups					
P-value	0.2445	–	–	–	–
Home morning BP at the end of treatment					
n	63	71	62	70	68
Patients who achieved the target BP [*n* (%)][b]	43 (68.3)	41 (57.7)	27 (43.5)	4 (5.7)	4 (5.9)
Differences in the proportion of the triple therapy groups to the dual therapy group					
P-value	0.0054	0.1022	–	–	–
Differences in the proportion of the triple therapy groups to their corresponding HCTZ monotherapy groups					
P-value	< 0.0001	< 0.0001	–	–	–
Differences in the proportion between the triple therapy groups					
P-value	0.2094	–	–	–	–
Home evening BP at the end of treatment					
n	55	62	50	57	49
Patients who achieved the target BP [*n* (%)][b]	49 (89.1)	52 (83.9)	34 (68.0)	11 (19.3)	6 (12.2)
Differences in the proportion of the triple therapy groups to the dual therapy group					
P-value	0.0080	0.0480	–	–	–
Differences in the proportion of the triple therapy groups to their corresponding HCTZ monotherapy groups					
P-value	< 0.0001	< 0.0001	–	–	–
Differences in the proportion between the triple therapy groups					
P-value	0.4121	–	–	–	–

AML, amlodipine besilate; AZI, azilsartan; BP, blood pressure; HCTZ, hydrochlorothiazide; LOCF, last observation carried forward.
[a]Patients who achieved the target BP was defined as patients who had systolic blood pressure of <140 mmHg and diastolic blood pressure of <90 mmHg.
[b]Patients who achieved the target BP was defined as patients who had systolic blood pressure of <135 mmHg and diastolic blood pressure of <85 mmHg.

Time profiles of the mean plots of the HBP in the morning at each time-point for each treatment group are shown in Fig. 3.

After 12.5 or 6.25 mg of HCTZ was added to AZI/AML 20/5 mg from week 2, further reductions were observed in HBP in both triple therapy groups.

The proportion of patients who achieved the target HBP (HDBP of <85 mmHg and HSBP of <135 mmHg) at the end of treatment is shown in Table 3.

The proportion of patients who achieved the target HBP was 68.3% (43/63 patients) in the AZI/AML/HCTZ 20/5/12.5 mg group, 57.7% (41/71 patients) in the AZI/AML/HCTZ 20/5/6.25 mg group, and 43.5% (27/62 patients) in the AZI/AML 20/5 mg group. A significant difference was observed between the AZI/AML/HCTZ 20/5/12.5 mg group and the AZI/AML 20/5 mg group, and between the triple therapy groups and their corresponding HCTZ monotherapy groups. A similar trend was observed when HBP in the evening was measured.

Safety

The incidences of overall AEs, serious adverse events (SAEs), and AEs that occurred in at least 2% of patients in each treatment group (safety analysis set) are shown in Table 4.

AEs that occurred in at least 2% of patients in the triple therapy groups were blood uric acid increased (16.4%), dizziness postural (10.4%), nasopharyngitis (6.0%), pharyngitis (6.0%), blood triglycerides increased (6.0%), eczema (6.0%), blood urea increased (3.0%), blood urine present (3.0%), and dizziness (3.0%) in the AZI/AML/HCTZ 20/5/12.5 mg group, and dizziness postural (9.3%), nasopharyngitis (5.3%), blood uric acid increased (4.0%), blood potassium increased (4.0%), contusion (2.7%), blood urea increased (2.7%), back pain (2.7%), and upper respiratory tract inflammation (2.7%) in the AZI/AML/HCTZ 20/5/6.25 mg group. No AEs of orthostatic hypotension were reported in this study. Among these AEs, the incidence of dizziness postural in the triple therapy groups was slightly higher than that in the other treatment groups. However, most of these AEs were considered to be mild in intensity and all were confirmed to have resolved. No other AEs of a markedly higher frequency in the triple therapy groups than the other treatment groups were observed.

With respect to AEs associated with hyperuricemia, which is commonly considered to be related to the

Table 4 Incidence of overall adverse events and incidence of adverse events that occurred in 2% or more patients in any treatment groups (safety analysis set)

	Triple therapy		Dual therapy	HCTZ monotherapy	
System organ class preferred term	AZI/AML/HCTZ 20/5/12.5 mg ($n=67$)	AZI/AML/HCTZ 20/5/6.25 mg ($n=75$)	AZI/AML 20/5 mg ($n=67$)	HCTZ 12.5 mg ($n=73$)	HCTZ 6.25 mg ($n=71$)
Overall AEs	37 (55.2)	34 (45.3)	25 (37.3)	31 (42.5)	34 (47.9)
Overall study drug-related AEs	15 (22.4)	10 (13.3)	3 (4.5)	14 (19.2)	3 (4.2)
Overall SAEs	0 (0.0)	0 (0.0)	2 (3.0)	1 (1.4)	2 (2.8)
Overall study drug-related SAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	3 (4.5)	2 (2.7)	0 (0.0)	2 (2.7)	4 (5.6)
Diarrhea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.8)
Infections and infestations	11 (16.4)	6 (8.0)	9 (13.4)	6 (8.2)	9 (12.7)
Nasopharyngitis	4 (6.0)	4 (5.3)	4 (6.0)	4 (5.5)	3 (4.2)
Pharyngitis	4 (6.0)	0 (0.0)	2 (3.0)	0 (0.0)	1 (1.4)
Injury, poisoning, and procedural complications	2 (3.0)	3 (4.0)	5 (7.5)	1 (1.4)	3 (4.2)
Fall	0 (0.0)	1 (1.3)	3 (4.5)	0 (0.0)	2 (2.8)
Contusion	0 (0.0)	2 (2.7)	1 (1.5)	1 (1.4)	1 (1.4)
Laceration	0 (0.0)	0 (0.0)	2 (3.0)	0 (0.0)	0 (0.0)
Investigations	17 (25.4)	12 (16.0)	6 (9.0)	15 (20.5)	9 (12.7)
Blood uric acid increased	11 (16.4)	3 (4.0)	0 (0.0)	13 (17.8)	3 (4.2)
Blood triglycerides increased	4 (6.0)	1 (1.3)	1 (1.5)	1 (1.4)	0 (0.0)
Blood urea increased	2 (3.0)	2 (2.7)	0 (0.0)	0 (0.0)	1 (1.4)
Blood potassium decreased	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	2 (2.8)
Blood potassium increased	0 (0.0)	3 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood urine present	2 (3.0)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Protein urine present	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)	2 (2.8)
Musculoskeletal and connective tissue disorders	3 (4.5)	3 (4.0)	2 (3.0)	2 (2.7)	4 (5.6)
Back pain	1 (1.5)	2 (2.7)	0 (0.0)	0 (0.0)	1 (1.4)
Nervous system disorders	9 (13.4)	8 (10.7)	2 (3.0)	4 (5.5)	3 (4.2)
Dizziness postural	7 (10.4)	7 (9.3)	1 (1.5)	0 (0.0)	0 (0.0)
Headache	1 (1.5)	1 (1.3)	0 (0.0)	2 (2.7)	3 (4.2)
Dizziness	2 (3.0)	1 (1.3)	0 (0.0)	1 (1.4)	0 (0.0)
Respiratory, thoracic, and mediastinal disorders	1 (1.5)	3 (4.0)	1 (1.5)	1 (1.4)	4 (5.6)
Upper respiratory tract inflammation	0 (0.0)	2 (2.7)	1 (1.5)	0 (0.0)	3 (4.2)
Skin and subcutaneous tissue disorders	5 (7.5)	5 (6.7)	2 (3.0)	7 (9.6)	2 (2.8)
Eczema	4 (6.0)	1 (1.3)	1 (1.5)	4 (5.5)	0 (0.0)
Rash	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.7)	0 (0.0)

Data are presented as the *n* (%) of patients.
AE, adverse event; AML, amlodipine besilate; AZI, azilsartan; HCTZ, hydrochlorothiazide; SAE, serious adverse event.

administration of HCTZ, 'blood uric acid increased' and 'hyperuricemia' were reported. There were no marked differences in the incidences of these AEs between each triple therapy group and its corresponding HCTZ monotherapy group.

SAEs were reported in five patients (11 events). No SAEs were reported in any of the triple therapy groups. There were no drug-related SAEs during the study.

No deaths were reported during the study. There were no remarkable findings of clinical concern with respect to the laboratory results, vital signs, weight, or 12-lead ECG findings.

Overall, AZI/AML/HCTZ triple therapy had acceptable safety profiles in patients with essential hypertension in this study.

Discussion

This study was carried out to evaluate the efficacy and safety of AZI/AML/HCTZ triple therapy compared with AZI/AML dual therapy and HCTZ monotherapy in Japanese patients with essential hypertension. The changes in the ODBP and OSBP at week 10 (LOCF) were evaluated as the efficacy endpoints. The reductions in the ODBP and OSBP at week 10 (LOCF) in patients who received the triple therapy with 12.5 mg of HCTZ were significantly greater than those in patients who received AZI/AML dual therapy or its corresponding HCTZ monotherapy. The proportion of patients who achieved the target OBP (ODBP of <90 mmHg and OSBP of <140 mmHg) at week 10 (LOCF) was the highest in the AZI/AML/HCTZ 20/5/12.5 mg group [92.5% (62/67 patients)]. In terms of safety, no AEs except postural dizziness showed an increased frequency in the triple therapy groups. Most events of postural dizziness were also considered to be mild in intensity and all were confirmed to have resolved during treatment or after study drug discontinuation. These data indicate that AZI/AML/HCTZ 20/5/12.5 mg triple therapy has acceptable safety profiles and that it is a beneficial treatment option for patients who need stricter BP control.

In the current study, HBP monitoring was assessed as an exploratory endpoint. The importance of HBP monitoring has been highlighted recently in the treatment of hypertension. It is considered that HBP monitoring can provide more information on BP compared with OBP because the data of more time-points are available. In addition, it can be obtained at certain fixed time points under certain fixed conditions over a long period of time, and thus the mean HBP values obtained with such data are less variable and have high reproducibility. The results obtained in the current study may provide be important for HBP measurement by automated telemetry.

The reduction in HBP at the end of treatment was similar to the OBP results; the reduction in both HDBP and HSBP in the AZI/AML/HCTZ 20/5/12.5 mg group was significantly greater than in the AZI/AML dual therapy or the corresponding HCTZ monotherapy groups. The proportion of patients who achieved the target HBP (HDBP of <85 mmHg and HSBP of <135 mmHg) at the end of treatment was also similar to the results of OBP; that is, the proportion was the highest in the AZI/AML/HCTZ 20/5/12.5 mg group [68.3% (43/63 patients)]. Similar to OBP, these HBP data also indicate that AZI/AML/HCTZ 20/5/12.5 mg triple therapy is a beneficial treatment option for patients who need stricter BP control.

In addition to the differences in OBP measurements, the HBP measurements also showed statistically significant differences between the AZI/AML/HCTZ 20/5/6.25 mg group and the AZI/AML 20/5 mg group both in HDBP and in HSBP, and between the AZI/AML/HCTZ 20/5/12.5 mg group and the AZI/AML/HCTZ 20/5/6.25 mg group in HDBP. These results indicate that HBP measurement by automated telemetry could be a more sensitive method of detecting changes in BP, although further investigation is necessary to determine the usefulness of HBP measurement by automated telemetry in the treatment of hypertension.

The principal limitations of the present study are that only patients with essential hypertension with an OSBP of at least 150 and less than 180 mmHg and an ODBP of at least 95 and less than 110 mmHg (without cardiovascular disease or significant renal impairment) were eligible for enrollment, as well as a relatively short treatment duration, which precludes extrapolation to other categories of hypertensive patients and any definitive conclusions on target organ-protective effects. Another limitation is that the results of this study were not compared with data obtained by ambulatory BP monitoring and the effects of the triple therapy over 24 h were thus not found.

Conclusion

AZI/AML/HCTZ 20/5/12.5 mg triple therapy leads to greater antihypertensive effects than AZI/AML 20/5 mg dual therapy both in OBP and in HBP, and has acceptable safety profiles in Japanese essential hypertensive patients. It was also observed that HBP measurement by automated telemetry could detect changes in BP that were not detected in OBP measurement, although further investigation is needed.

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Conflicts of interest

H.R. served as the medical expert for this study and received honoraria from Takeda Pharmaceutical Company Limited for lectures given during the study period. H.R. also has the following actual conflicts of interest in relation to this presentation: lecture fees and research funding from various pharmaceutical companies in Japan that market antihypertensive drugs, including Takeda Pharmaceutical Company Limited. K.S., Y.S., Y.N., Y.K., and S.T. are employees of Takeda Pharmaceutical Company Limited.

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