Original Article

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The Efficacy of Single-pill Combination of Olmesartan Medoxomil and Amlodipine Besylate on Office Blood Pressure in Hypertensive Patients who did not Respond to Amlodipine Besylate Monotherapy

Byong-kyu Kim

Division of Cardiology, Department of Internal Medicine, Dongguk University College of Medicine, Gyeongju Hospital, Gyeongju, Republic of Korea

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Corresponding Author: Byong-kyu Kim, MD
Division of Cardiology, Department of Internal Medicine, Dongguk University College of Medicine, Gyeongju Hospital, 87 Dongdae-ro, Gyeongju 38067, Republic of Korea
Tel: +82-54-770-8563; Fax: +82-54-770-8529
E-mail: bleumatin@dongguk.ac.kr

Background: As combination therapy, switching to single-pill combination (SPC) medication after a short period of monotherapy is helpful because reducing pill numbers can improve patients' adherence to medications. This study was aimed to assess the effect of the single-pill combination (SPC) of olmesartan medoxomil 20 mg and amlodipine besylate 5 mg (OLM 20 mg/AML 5 mg) on blood pressure (BP) reduction in hypertensive patients who did not respond to amlodipine besylate 5 mg (AML 5 mg) monotherapy for 4 weeks.

Methods: This study was a prospective, open-label, multi-center, non-comparative study. Patients whose BP was not got the target BP (≥140 mmHg and if diabetic patients ≥130 mmHg) after 4 weeks treatment with AML 5 mg, were enrolled. AML 5 mg was switched to the SPC (OLM 20 mg/AML 5 mg) treatment for 8 weeks. The primary effectiveness endpoint was the reduction of seated systolic blood pressure (SeSBP) after SPC (OLM 20 mg/AML 5 mg) treatment for 8 weeks. The changes of brachial-ankle pulse wave velocity (baPWV), central BP (CBP), and augmentation index (AIx@75) were evaluated also.

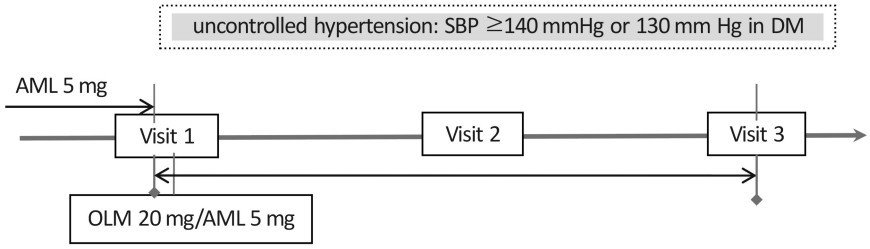
Results: Forty-seven patients were enrolled (mean age = 52±9 years, 36 men). After the SPC treatment for 8 weeks, SeSBP was reduced from 153±9 mmHg to 131±18 mmHg and seated diastolic BP (SeDBP) from 95±8 mmHg to 81±11 mmHg ($p<0.001$ and $p<0.001$, respectively). The reduction of SeSBP/SeDBP were 22 mmHg and 14 mmHg, respectively. The target goal BP achievement rate was 74.5%, and baPWV, CBP, and AIx@75 were improved.

Conclusion: SPC (OLM 20 mg/AML 5 mg) treatment for 8 weeks was effective in reducing BP, achieving target BP goal, and also improving arterial stiffness in uncontrolled hypertensive patients with AML 5 mg monotherapy.

Key Words: Hypertension, Antihypertensive agents, Drug combination, Blood pressure

INTRODUCTION

Hypertension is one of the major risk factors for cardiovascular disease (CVD), and a leading cause of death[1,2]. Achieving the target blood pressure (BP) is crucial in reducing the complications and mortality caused by hypertension[3,4]. In many patients, it is difficult to achieve the target blood pressure with monotherapy. Therefore, an increase in the dose or combination of different classes of antihypertensive drugs is required. As combination therapy, switching to single-pill combination (SPC) medication after a short period of monotherapy is helpful because a reduc-



Visit 1 (-2+0 week)	**Visit 2** (4 weeks±1 week)	**Visit 3** (8 weeks±1 week)
Screening and prescribe a test drug	Middle visit	Final visit
SeSBP/SeDBP PWV and CBP Laboratory test	SeSBP/SeDBP	SeSBP/SeDBP PWV and CBP Laboratory test

Fig. 1. Study protocol schedule.
SBP, systolic blood pressure; DM, diabetes mellitus; AML, amlodipine besylate; OLM, olmesartan medoxomil; SeSBP, seated systolic blood pressure; SeDBP, seated diastolic blood pressure; PWV, pulse wave velocity; CBP, central blood pressure.

tion of pill numbers can improve patients' adherence to medications. Recently, many guidelines recommended SPC therapy as an initial treatment to achieve the target BP[3,4]. The purpose of the study was to examine the effects of the SPC of Olmesartan (OLM) 20 mg and amlodipine (AML) 5 mg on BP reduction in hypertensive patients who did not respond to AML 5 mg monotherapy for 4 weeks.

METHODS

1. Study population and protocol

This study was a prospective, open-label, multi-center, non-comparative study, and investigator-initiated and sponsored one. Forty-seven patients with uncontrolled BP were enrolled and visited Dongguk University Hospital and Daegu Catholic University Hospital in Korea from June 2015 to August 2016 (26 patients at Dongguk University Hospital, 21 patients at Daegu Catholic University Hospital). The uncontrolled BP was defined as seated systolic BP (SeSBP) ≥ 140 mmHg or SeSBP ≥130 mmHg in diabetic patients after AML 5 mg treatment for 4 weeks. The inclusion and exclusion criteria are described in the supplement.

Primary effectiveness endpoint was reduction of SeSBP after SPC (OLM 20 mg/AML 5 mg) medication for 8 weeks from baseline. And secondary effectiveness endpoint was target SeSBP attaining rate after SPC (OLM 20 mg/AML 5 mg) treatment for 8 weeks.

All patients were measured Brachial-ankle pulse wave velocity (baPWV), CBP, and AIx@75 at baseline and after 8 weeks SPC (OLM 20 mg/AML 5 mg) treatment.

All patients took the scheduled dosage of single tablet (OLM 20 mg/AML 5 mg) once a day for 8 weeks, and other antihypertension medications were prohibited during this study. All patients were taken laboratory tests included renal profiles, lipid profiles, hepatic profiles, random serum glucose, glycosylated hemoglobin (HbA1c), uric acid, and high sensitivity C reactive protein (hsCRP), urine dipstick test at baseline and the final visit of the study (8 weeks).

The protocol was approved by the Institutional review board of Dongguk University Gyeongju Hospital in and Daegu Catholic University Hospital (IRB No. 11-10, IRB No. CR-11-033). All of the patients gave written informed consent. Overall protocol was described in Figure 1.

2. Measurement of office blood pressure, brachial-ankle pulse wave velocity, and central blood pressure

After rest for at least 5 minutes, brachial BP was measured two times at 1-2 minutes interval. The arm with higher SBP at the screening visit was designated as the index arm. During the next visit, the BP was measured in the index arm.

The average value was considered as the BP at the visit. The validated oscillometric BP device (WatchBP Home, Microlife, Taiwan) was used for BP measurement at the first visit, 4th week, and 8th week visit. A baPWV was measured in a quiet room controlled at 22±1℃. And all patients asked to visit for test overnight fasted state. All patients asked to stop drinking caffeine-containing beverages, drinking alcohol and smoking at least 12 hours before test. After 15-minute rest, baPWV was measured using an automated device (VP-1000; Colin, Co. Ltd, Komaki, Japan) in the supine position[5]. After 10-minute rest, CBP and augmentation index (AIx) were measured in the sitting using a commercially available radial artery tonometry device (SphygmoCor®; AtCor Medical, Sydney, Australia), Radial artery applanation tonometry was conducted using a hand-held tonometer over the radial artery and applying mild pressure to partially flatten the artery. AIx@75 that was adjusted AIx assuming a heart rate was 75 beats per minute was obtained. Measurements were taken at baseline and after 8 weeks treatment period.

3. Statistical Analysis

Based on the existing literature, the difference between the reference group (AML 5 mg) and after 8 weeks SPC (OLM 20 mg/AML 5 mg) treatment was -0.29 mmHg, and the maximum standard deviation was set to ± 0.7 mmHg. So, this study should need 36 patients at 5% significance level and 80% power[6]. Therefore, the total number of patients required 45 patients assuming the dropout rate of 20%[6].

Continuous variables are presented as the mean ± standard deviation and compared with paired t-test and repeated ANCOVA, and categorical variables are compared by performing the chi-square test. A p-value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS Version 20.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

Forty-seven patients were enrolled in this study. The mean age of the patients was 52±9 years (range: 43-61 years). Men were 36 (77%), and women were 11 (23%). On the previous medical history, 1 patient (2.1%) had diabetes mellitus, and 4 patients (8.5%) had dyslipidemia. The mean body mass index (BMI) was 26.1±4.4 kg/m^2 (range: 21.7-30.5) (Table 1).

In the laboratory findings, there were no statistically significant change in creatinine, estimated glomerular filtration rate (eGFR), Total cholesterol, high-density lipoprotein (HDL)-cholesterol, aspartate transaminase (AST), alanine transaminase (ALT), serum glucose, HbA1c, uric acid, and hsCRP, proteinuria after 8-weeks treatment from baseline. However, only low-density lipoprotein (LDL)-cholesterol decreased significantly at 8-weeks of treatment from baseline (Table 2).

After the SPC treatment, SeSBP was reduced from 153±9

Table 1. Baseline clinical characteristics

	Number (%)
Total	47
Age	52±9
Men	36 (77)
DM	1 (2.1)
Dyslipidemia	4 (8.5)
BMI (kg/m^2)	26.1±4.4

DM, diabetes mellitus; BMI, body mass index

Table 2. Laboratory findings of baseline and after 8 weeks SPC (OLM 20 mg/AML 5 mg) medication

	Baseline	At week 8	p value
Creatinine (mg/dl)	0.8±0.1	0.9±0.2	0.906
eGFR	98.3±13.2	99.9±13.9	0.588
Total cholesterol (mg/dl)	200±40	192±26	0.147
TG (mg/dl)	146±81	157±93	0.787
LDL-cholesterol (mg/dl)	138±38	125±31	0.01
HDL-cholesterol (mg/dl)	56±12	54±12	0.395
AST (mg/dl)	31±15	28±12	0.228
ALT (mg/dl)	33±19	29±14	0.138
Serum glucose (mg/dl)	106±38	103±28	0.587
HbA1c (%)	6.0±0.8	6.0±0.7	0.541
Uric acid (mg/dl)	5.3±1.7	5.5±1.7	0.366
hsCRP (mg/dl)	0.21±0.32	0.13±0.14	0.084
Proteinuria			
- 0	39 (84.8%)	37 (90.2%)	0.244
- Trace	2 (4.3%)	4 (9.8%)	
- 1+	2 (4.3%)	0 (0.0%)	
- 2+	2 (4.3%)	0 (0.0%)	
- 3+	0 (0.0%)	0 (0.0%)	
- 4+	1 (2.2%)	0 (0.0%)	

eGFR, estimated glomerular filtration rate; TG, triglyceride; LDL, low density lipoprotein; HDL, high density lipoprotein; AST, aspartate transaminase; ALT. alanine transaminase; HbA1c, hemoglobin A1c; hsCRP, high sensitivity c-reactive protein.

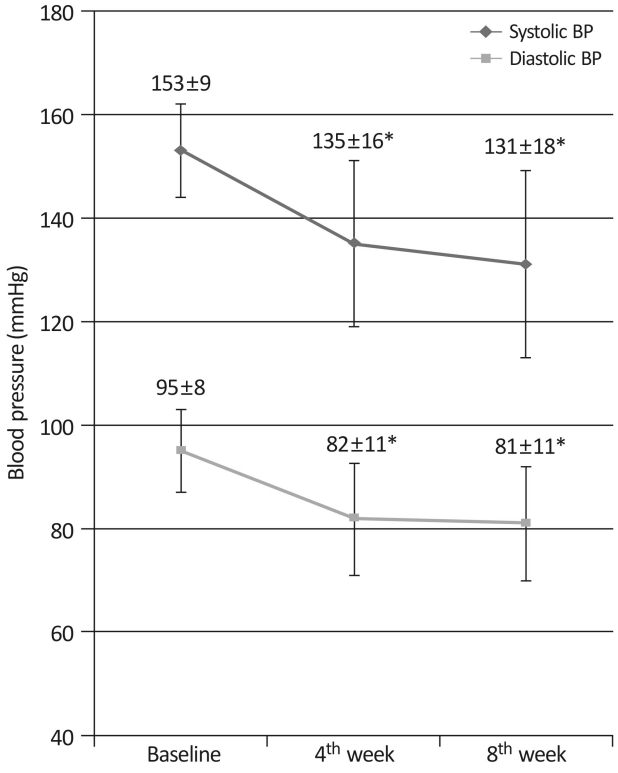


Fig. 2. Mean seated blood pressure over the treatment *p<0.001 baseline vs. 4th and 8th week. BP, Blood pressure.

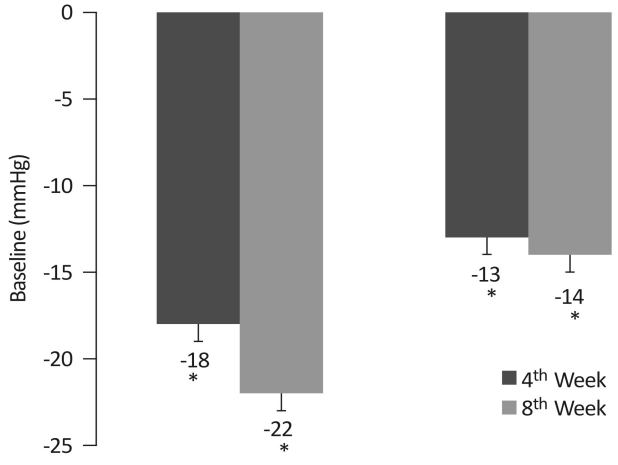


Fig. 3. Change from baseline in seated SBP and DBP (±SE of the mean) over the treatment. *p<0.001. SeSBP, seated systolic blood pressure; SeDBP, seated diastolic blood pressure.

mmHg to 135±16 mmHg at 4th week and 131±18 mmHg at 8th week (p<0.001 and p<0.001, respectively). And SeDBP was also reduced from 95±8 mmHg to 82±11 mmHg at 4th week and 81±11 mmHg at 8th week (p < 0.001 and p<0.001, respectively) (Fig. 2). After the SPC treatment, SeSBP reduction was 18 mmHg at 4 week and 22 mmHg at 8 week, respectively (p<0.001). SeDBP reduction was 13 mmHg at 4 week and 14 mmHg at 8 week, respectively (p<0.001) (Fig. 3). After the 8-weeks SPC treatment, the target systolic blood pressure (SBP) goal achievement rate was 74%, and the diastolic blood pressure (DBP) goal achievement rate was 82.9% (Fig. 4).

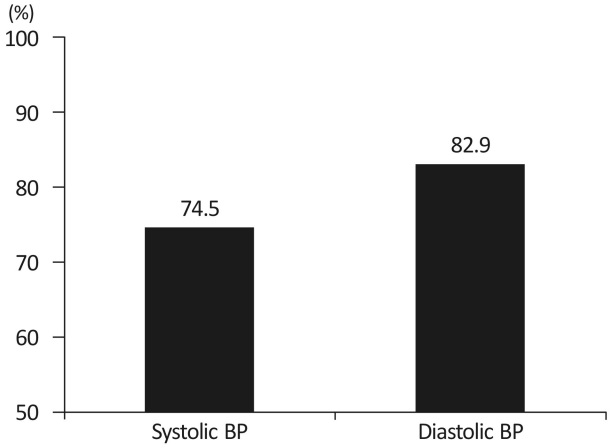


Fig. 4. Target blood pressure achievement rate after 8 weeks treatment with single pill combination drug.

Table 3. The differences of blood pressure and PWV, AIx between baseline and after 8 weeks treatment of single pill combination of olmesartan medoxomil 20 mg and amlodipine besylate 5 mg

Parameters	Baseline	At week 8	p value
SeSBP (mmHg)	153±9	131±18	0.001
SeDBP (mmHg)	95±8	80±11	0.001
baPWV (cm/sec)	1,494±262	1,279±140	<0.001
Central SBP (mmHg)	144±13	120±13	<0.001
Central DBP (mmHg)	98±7	83±10	<0.001
AIx@75 (%)	27±9	21±10	<0.001

SeSBP, sitting systolic blood pressure; SeDBP, sitting diastolic blood pressure; baPWV, brachial-ankle pulse wave velocity; SBP, systolic blood pressure; DBP, diastolic blood pressure; AIx, augmentation index; AIx@75, augmentation index adjusted assuming heart rate was 75 beats per minute

The SPC treatment for 8 weeks reduced baPWV from 1,494±262 cm/sec to the 1,279±140 cm/sec, and also reduced CBP and AIx@75 significantly (p<0.001) (Table 3).

At the 4th week, there were no adverse events two cases of adverse events were but those were not related to study drug. And there was no adverse reaction and adverse event were observed at 8th week. In this study, no severe sympto-

Table 4. The clinical characteristics between the group that achieved the target blood pressure goal and the group that did not achieve.

Target BP Goal achievement	No (N=12)	Yes (N=35)	p value
Sex			0.301
- Women	1 (8.3%)	10 (28.6%)	
- Men	11 (91.7%)	25 (71.4%)	
Age	48.3±13.5	52.9±7.5	0.290
BMI	27.4±5.0	25.7±4.2	0.283
SeSBP (mmHg)	157.3±11.3	151.5±8.0	0.056
SeDBP (mmHg)	97.7±10.3	93.4±7.1	0.120
DM			0.571
- No	11 (91.7%)	35 (100.0%)	
- Yes	1 (8.3%)	0 (0.0%)	
Dyslipidemia			0.532
- No	12 (100.0%)	31 (88.6%)	
- Yes	0 (0.0%)	4 (11.4%)	
Creatinine (mg/dl)	0.9±0.2	0.8±0.2	0.264
eGFR	98.8±17.1	98.2±11.9	0.904
AST (mg/dl)	25.8±5.8	31.9±15.7	0.060
ALT (mg/dl)	25.8±10.5	33.0±19.9	0.123
Total cholesterol (mg/dl)	179.9±18.9	206.7±42.6	0.008
TG (mg/dl)	160.5±114.7	144.4±80.5	0.597
LDL-cholesterol (mg/dl)	116.8±21.7	141.3±40.5	0.015
HDL-cholesterol (mg/dl)	51.1±15.8	57.2±12.4	0.191
Serum glucose (mg/dl)	127.8±66.2	100.9±16.9	0.192
hsCRP (mg/dl)	0.1±0.1	0.2±0.3	0.056
Uric acid (mg/dl)	5.3±1.1	5.3±1.9	0.891
HbA1c (%)	6.2±1.1	5.9±0.6	0.410
Proteinuria			0.297
- 0	9 (75.0%)	30 (88.2%)	
- Trace	1 (8.3%)	1 (2.9%)	
- 1+	0 (0.0%)	2 (5.9%)	
- 2+	1 (8.3%)	1 (2.9%)	
- 3+	0 (0.0%)	0 (0.0%)	
- 4+	1 (8.3%)	0 (0.0%)	

BMI, body mass index; SeSBP, seated systolic blood pressure; SeDBP, seated diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; AST, aspartate transaminase; ALT. alanine transaminase; TG, triglyceride; LDL, tow density lipoprotein; HDL, high density lipoprotein; hsCRP, high sensitivity c-reactive protein; HbA1c, hemoglobin A1c

matic hypotension or syncope, were observed. Furthermore, there were no cases where participants withdrew from the study due to adverse reactions.

There was significant difference in baseline total cholesterol and LDL-cholesterol between the patients that achieved the target blood pressure goal and the patients that did not (Table 4).

DISCUSSION

The present study demonstrated that the fixed-dose SPC (OLM 20 mg/AML 5 mg) treatment for 8 weeks effectively reduced BP, achieved target BP. In addition, central BP was reduced, and arterial stiffness was improved in uncontrolled hypertensive patients with AML 5 mg monotherapy. The 8 weeks SPC treatment reduced SeSBP/SeDBP 22 mmHg and 14 mmHg respectively. The target goal achievement rate was 74.5% for SeSBP and 82.9% for SeDBP. These results support that SPC can be very effective in controlling BP in patients with uncontrolled hypertension with amlodipine 5 mg monotherapy. Poorly controlled hypertension could be related to multiple factors including low antihypertensive efficacy of single drug therapies, reluctance of primary care physicians to modify/titrate initially chosen therapy, and poor compliance with medication[7]. Many hypertension guidelines recommend combination therapy for the treatment of high BP ≥150 mmHg and combination of standard dose of two drugs as the initial management in mild/moderate arterial hypertension[3,4]. They also encourage to use SPC. The clinical guidelines are conveying messages that using fixed dose combination therapies to control hypertension may be more effective than monotherapy with regular dose, leading to better control of BP and reducing cardiovascular/cerebrovascular morbidity and mortality caused by hypertension in the population[3,4,7].

Arterial stiffness has been known to be an important independent risk factor for cardiovascular disease in hypertensive patients[8]. Arterial stiffness can be easily estimated by using measurement of pulse wave velocity (PWV) and augmentation index. In addition, CBP was more closely related to the occurrence of cardiovascular disease than the brachial arterial BP[9-14]. Clinical studies had shown that central SBP and pulse pressure were more useful for prediction of cardiovascular events than brachial artery BP[15].

SPC treatment reduced baPWV, CBP and AIx significantly from baseline at week 8, indicating an improvement of arterial stiffness. It is unclear whether the reduced arterial stiffness and CBP with short-term treatment with SPC may im-

prove cardiovascular outcomes. However, more effective BP control and reduction of arterial stiffness may increase the satisfaction of both physicians and patients. This will lead to improved adherence to treatment and BP control and, eventually reduction of cardiovascular events.

There were no statistically significant differences in creatinine, eGFR, total cholesterol, HDL-cholesterol, AST, ALT, Serum glucose, HbA1c, uric acid, and hsCRP, proteinuria between baseline and at week 8, except significantly reduced LDL-cholesterol. These results suggest SPC (OLM 20 mg/AML 5 mg) was a safe and well-tolerated fixed-dose single pill combination medication.

There were no significant differences in clinical characteristics between the group that achieved the target blood pressure and the group that did not except total cholesterol and LDL-cholesterol. The reason for these results were thought to be as follows, there were a higher number of dyslipidemia patients, and as a result, their total cholesterol and LDL-cholesterol levels were higher compared to those who did not achieve the target BP and small number of study subjects also.

Although statistically insignificant, baseline SeSBP of the group that did not achieve the target goal BP had about 7 mmHg higher than that of group that achieved the target goal BP. Considering the small sample size of the study, 7 mmHg difference could be clinically relevant because the change to SPC (OLM 20 mg/AML 5 mg) can be considered in patients with SeSBP <155 mmHg after 4 weeks AML 5 mg monotherapy, but not in patients with SeSBP ≥155 mmHg. Patients with a SeSBP ≥155 mmHg are more likely to require three of more antihypertensive drugs with higher doses to achieve the target BP goal. This should be evaluated in further studies.

There were limitations to this study. The number of subjects was small. The follow-up period was short. Moreover, the single-arm design of the study did not allow comparing BP lowering effect of SPC treatment to other treatment.

In conclusion, SPC (OLM 20 mg/AML 5 mg) treatment for 8 weeks was effective in reducing BP, achieving target BP goal and improving arterial stiffness in uncontrolled hypertensive patients with AML 5 mg monotherapy. SPC treatment for 8 weeks was safe and well tolerated. But further large scaled and comparative design studies are needed to confirm these results and evaluate long-term outcomes.

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Conflict of interest

B.K. Kim has received lecture honorarium from Daewoong Co., Ltd. and Daiichi-Sankyo Korea Ltd.

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SUPPLEMENT

Inclusion criteria are defined as follows.

1. Male and female patients aged 20 to 80
2. Uncontrolled hypertensive patients who meet the following conditions:
   1) Uncontrolled hypertension is Amlodipine (Amlodipine besylate) 5 mg monotherapy for 4 weeks
   2) Average seated systolic blood pressure (SeSBP) of at least 140 mmHg after treatment for at least 4 weeks (diabetic patients' case average SeSBP $\geq$130 mmHg)
   3) Patients who voluntarily consented to participate in this clinical trial

Exclusion criteria are defined as follows.

1. Secondary hypertension patients (renovascular hypertension, aortic coarctation, pheochromocytoma, primary aldosteronism, etc.).
2. Patients with mean SeSBP greater than 180 mmHg or mean sitting diastolic blood pressure (SeDBP) greater than 110 mmHg at the screening.
3. Patients whose SeSBP difference of the selected arm greater than 20 mmHg or SeDBP difference of the selected arm greater than 10 mmHg at the screening.
4. Patients with hypertensive encephalopathy, unstable angina, transient ischemic attack, acute myocardial infarction, severe aortic stenosis, severe congestive heart failure or any type of angioplasty within the last 6 months.
5. Patients with heart failure, 2nd or 3rd degree atrioventricular block, severe arrhythmia or valve heart disease.
6. Patients with severe cardiovascular, cerebrovascular, gastrointestinal or hematologic disease.
7. Severe renal failure, patients with unilateral or bilateral renal artery stenosis, kidney transplanted patients, patients with only one kidney, patients with dialysis
8. Patients with severe liver failure, patients with biliary obstruction, or patients with confirmed liver disease based on past data.
9. Patients with uncorrected sodium or fluid depletion.
10. Patients with hypersensitivity to ingredients contained in this test drug, such as amlodipine besylate or other dihydropyridine drugs and olmesartan medoxomil.
11. Tumor patients.
12. Patients with uncontrolled neurological and psychiatric conditions
13. Pregnant women, lactating mothers, women who have a plan for pregnancy or may become pregnant
14. If patients have participated in another clinical trial within the past month
15. Patients who are judged by investigators to have difficulty performing this clinical trial or have medical findings that do not meet the clinical trial.