Efficacy and safety of olmesartan medoxomil-amlodipine besylate tablets (Sevikar®) in older patients with essential hypertension: Subgroup analysis from the Sevikar study

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Abstract. Essential hypertension is a notable threat for the older (age, ≥65 years) population. However, to the best of our knowledge, a real-world study assessing olmesartan medoxomil-amlodipine besylate (OM-AML) tablets in older Chinese patients with essential hypertension has not been performed. Therefore, the present study aimed to evaluate the efficacy and safety of OM-AML tablets in these patients. A total of 463 older Chinese patients with essential hypertension treated with OM-AML (20/5 mg) tablets (Sevikar®) were analyzed in a prospective, single-arm, multi-center, real-world study. Seated systolic blood pressure (SeSBP) and seated diastolic blood pressure (SeDBP) at baseline, and at week (W)4 and W8 after OM-AML tablet administration were measured. The mean ± standard error change of SeSBP/SeDBP was -10.3±0.8/-4.6±0.5 and -12.5±0.8/-5.6 ±0.5 mmHg at W4 and W8, respectively. At W4, 74.1 and 26.8% of patients achieved BP target according to the China and American Heart Association (AHA) criteria, while at W8, 78.0 and 38.7% of patients reached these BP targets accordingly. Finally, 76.5 and 80.5% of patients achieved BP response at W4 and W8, respectively. Furthermore, home-measured SeSBP and SeDBP were significantly decreased from W1 to W8 (both P<0.001). Additionally, the satisfaction of both patients and physicians was elevated at W8 compared with at W0 (both P<0.001). The medication possession rate from baseline to W4 and W8 was 95.5 and 92.5%. The most common drug-associated adverse events by system organ classes were nervous system disorder (4.5%), vascular disorder (2.8%), and general disorder and administration site conditions (2.6%), which were generally mild. In conclusion, OM-AML tablets may be considered effective and safe in lowering BP, enabling the achievement of guideline-recommended BP targets in older Chinese patients with essential hypertension.

Introduction

Essential hypertension is a highly prevalent chronic disease with >30% of adults having hypertension in 2010 globally; the disease is associated with cardio- and cerebrovascular diseases, such as stroke, myocardial infarction and heart failure (1,2). It has been reported that essential hypertension is more prevalent in the older (age ≥65 years) population compared with young adults or middle-aged subjects, partially due to arterial stiffness, worse renal function and comorbidities observed in older individuals (3,4). Considering the aging population and the increase in life expectancy, essential hypertension in older adults may pose a critical burden on the public health system in the future (5-7). Regarding the pharmacological management of essential hypertension in older patients, numerous factors should be taken into consideration, including contraindications due to comorbidity, frailty and ability to follow medical instructions. Therefore, more alternative routes of pharmacological management are needed for these patients (3,8,9).

Olmesartan medoxomil-amlodipine besylate (OM-AML) tablets are a dose-fixed antihypertensive drug, containing an angiotensin receptor blocker (OM) and a calcium channel blocker (AML) (10,11). Compared with combined administration of OM and AML tablets, dose-fixed OM-AML tablets are more convenient and can promote drug adherence (12). Currently, dose-fixed antihypertensive drugs are recommended by several guidelines, including guidelines from the World Health Organization, American College of Cardiology and American Heart Association, and European Society Of Hypertension-European Society Of Cardiology (13,14). According to previous studies, OM-AML tablets exhibit better efficacy in controlling blood pressure (BP) compared with OM or AML monotherapy (15-17). This could be due to the fact that OM-AML tablets not only combine two effective antihypertensive drugs, but also improve patient compliance due to convenience (18). However, the majority of studies evaluating the efficacy and safety of OM-AML tablets have been performed in Western countries, with Caucasian, Hispanic and Black individuals being the primary study subjects (15-17). Since China accounts for a large proportion of hypertensive individuals globally (7), it is necessary to evaluate OM-AML tablets in Chinese patients with essential hypertension.

Therefore, the current prospective, multicenter, real-world study aimed to evaluate the efficacy and safety of OM-AML tablets in older (age, ≥65 years) Chinese patients with essential hypertension.

Materials and methods

Study population. A subgroup analysis of 463 older patients with essential hypertension from the Sevikar® (SVK) study was performed. The SVK study was a prospective, single-arm, multicenter, real-world study aiming to investigate the efficacy and safety of SVK in patients with essential hypertension in China. A detailed description of the SVK study design is available in the Chinese Clinical Trial Registry (chictr.org.cn/; registration no., ChiCTR1900026574). A total of 463 older patients were screened from the SVK study based on the following criteria: i) Patients diagnosed with essential hypertension; ii) aged ≥65 years; iii) treated with SVK as antihypertensive therapy; iv) with at least one follow-up BP measurement in addition to baseline measurement and v) signed informed consent. The present study was approved by the Ethics Committee of Zhongshan Hospital, Fudan University (approval no. B2019-174R2; Shanghai, China).

Administration of medication. SVK [Daiichi Sankyo (Shanghai) Holdings Co., Ltd.] was a compound preparation; each SVK tablet contained 20 mg OM and 5 mg AML. The dose of SVK recommended by the physicians was one oral tablet once a day.

Measurement. The seated diastolic BP (SeDBP) and seated systolic BP (SeSBP) of patients were measured at baseline (week 0, W0) and then at W4±7 days (W4) and W8±7 days (W8) in outpatient clinics. From the first day of medication, the patients measured their BP every day (home-measured BP). Furthermore, the daily medication-taking of patients and adverse events (AEs) were recorded to determine the medication possession rate (MPR) and safety profiles. Additionally, both attending physicians and patients scored satisfaction with the current hypertension treatment at W0 and W8 using

a 10-cm visual analogue scale (VAS) (19); a higher score indicated higher satisfaction.

Outcomes and definitions. The outcomes included mean change in SeDBP and SeSBP from W0 to W8, proportion of patients achieving American Heart Association (AHA) and China BP targets (20,21), proportion of patients achieving BP response, changes in home-measured BP from W0 to W8, change in physician and patient satisfaction with hypertension treatment (VAS) from W0 to W8, MPR and onset of AEs. The AHA BP target was defined as SeSBP <130 mmHg and SeDBP <80 mmHg (20). The China BP target was defined as SeSBP and SeDBP <140 and <90 mmHg, respectively (21). The BP response rate was defined as proportion of patients who achieved SeSBP <140 mmHg (or a decrease of ≥20 mmHg) and SeDBP of <90 mmHg (or a decrease of ≥10 mmHg). MPR was calculated as follows: MPR=actual days of medication use/total number of days.

Statistical analysis. Statistical analysis was performed using R version 4.0.5 (r-project.org) and SPSS version 26.0 (IBM Corp.). Categorical data are expressed as number and percentage, and were analyzed using χ^2 or Fisher's exact test. Measured data are expressed as the mean ± SD or SEM, or median and interquartile range. Comparisons of the measured data were carried out by Mann Whitney U test or Kruskal-Wallis test. Data on blood pressure are usually presented as the mean ± SD in the field of hypertension, so this convention has been followed. Post hoc comparison for multiple groups was conducted by Bonferroni test. Related factors were screened using a logistic regression model. P<0.05 was considered to indicate a statistically significant difference.

Results

Patient characteristics. The mean ± SD age of patients was 70.4±4.1 years. In addition, a total of 238 (51.4%) female patients (mean age, 70.5±4.2 years) and 225 (48.6%) male patients (mean age, 70.4±4.0 years) were included. The median (IQR) time since hypertension diagnosis was 13.1 (6.1-21.2) years, while 259 (55.9%) patients had a family history of hypertension. At baseline, mean ± SD SeSBP and SeDBP were 142.8±16.7 and 82.1±10.2 mmHg, respectively. A total of 264 (57.0%) and 108 (23.3%) patients had abnormal SeSBP and SeDBP, respectively (defined as SeSBP ≥140 mmHg and SeDBP ≥90 mmHg, accordingly). Furthermore, 349 (75.4%) patients received OM-AML tablets without lipid-modifying agents or other medication (any medication apart from antihypertensive agents and lipid-modifying agents), 33 (7.1%) patients were co-treated with OM-AML tablets and lipid-modifying agents, while 81 (17.5%) patients received OM-AML tablets and lipid-modifying agents and other drugs. The main characteristics of patients are listed in Table I.

SeSBP and SeDBP are reduced after OM-AML treatment. The mean ± SD SeSBP and SeDBP values at W4 were 132.5±11.9 and 77.6±8.3 mmHg, respectively, which were decreased compared with at W0. At W8, mean ± SD SeSBP and SeDBP values were 130.8±11.8 and 76.5±7.7 mmHg, respectively, which were decreased compared with those recorded at W4 and W0 (Fig. 1A). In addition, the mean ± SEM change of SeSBP and SeDBP was -10.3±0.8 and -4.6±0.5 mmHg at W4 and -12.5±0.8 and -5.6±0.5 mmHg at W8 (Fig. 1B).

Comparison revealed greater changes in SeSBP or SeDBP in patients with shorter time since diagnosis of hypertension, patients with a history of allergy and kidney disease, patients without history of cardiovascular disease or dyslipidemia, patients with abnormal SeSBP and SeDBP at baseline, patients with moderate or severe hypertension, or patients without history of hypertension treatment and patients treated with OM-AML tablets and lipid-modifying agents (Table SI). Patients who continued their existing antihypertensive therapy (n=118) showed the most significant changes in SeSBP and SeDBP compared with patients without history of antihypertensive drugs (n=17) and those who discontinued existing antihypertensive therapy (n=328; Table SII).

BP target achievement was satisfactory after OM-AML treatment. At W4, 343 (74.1%) and 124 (26.8%) patients achieved BP targets according to the China or AHA criteria, respectively. Additionally, at W8 (n=431 due to lack of assessment data at W8 for some patients), 336 (78.0%) and 167 (38.7%) patients achieved the China and AHA criteria of BP target, respectively (Fig. 2A). A total of 355 (76.7%) and 434 (93.7%) patients at W4, and 347 (80.5%) and 410 (95.1%) patients at W8, met the China criteria of SeSBP and SeDBP target, respectively (Fig. 2B). A total of 183 (39.5%) and 255 (55.1%) patients at W4, as well as 204 (47.3%) and 274 (63.6%) patients at W8, achieved SeSBP and SeDBP targets according to AHA criteria, respectively (Fig. 2C). BP response rates of 76.5 and 80.5% were recorded at W4 and W8, respectively (Fig. 2D).

Subgroup analysis showed that female patients or patients with shorter time since hypertension diagnosis, normal SeSBP or SeDBP at baseline, a history of monotherapy of antihypertensive drugs or those treated with OM-AML tablets alone more significantly achieved China or AHA BP targets or BP response rate at W8 (Table II). Furthermore, male patients (vs. females), time since hypertension diagnosis of ≥10 were associated with a lower probability of achieving AHA BP target at W8. Abnormal SeSBP at baseline (vs. normal) and treatment with OM-AML tablets and lipid-modifying agents and other drugs (vs. OM-AML tablets without lipid-modifying agent or other drugs) were also independently associated with lower probability of achieving AHA BP target at W8 (Table SIII). In addition, abnormal SeSBP at baseline (vs. normal) and patient treatment with OM-AML tablets and lipid-modifying agents and other drugs (vs. OM-AML tablets without lipid-modifying agent or other drugs) were independently associated with lower probability of achieving China BP target at W8 (Table SIV). At W8 after the initiation of OM-AML tablet administration, the history of double combination of antihypertensive drugs (vs. monotherapy) and treatment with OM-AML tablets and lipid-modifying agents and other drugs (vs. OM-AML tablets without lipid-modifying agent or other drugs) were independently associated with lower BP response rate (Table SV).

Table I. Baseline characteristics (n=463).

Characteristic	Value
Mean age, years	70.4±4.1
Sex, n (%)	
Female	238 (51.4)
Male	225 (48.6)
Mean BMI, kg/m^2	25.2±3.1
Highest completed education level, n (%)	
Primary school or less	83 (17.9)
High school	269 (58.1)
Undergraduate or above	111 (24.0)
Smoker, n (%)	
No	339 (73.2)
Yes	124 (26.8)
Alcohol intake, n (%)	
No	408 (88.1)
Yes	55 (11.9)
Median (IQR) time since hypertension diagnosis, years	13.1 (6.1-21.2)
Family history of hypertension, n (%)	
No	185 (40.0)
Yes	259 (55.9)
Unknown	19 (4.1)
History of allergy, n (%)	
No	410 (88.6)
Yes	47 (10.2)
Unknown	6 (1.3)
History of respiratory disease, n (%)	
No	416 (89.8)
Yes	45 (9.7)
Unknown	2 (0.4)
History of kidney disease, n (%)	
No	432 (93.3)
Yes	30 (6.5)
Unknown	1 (0.2)
History of diabetes, n (%)	
No	358 (77.3)
Yes	102 (22.0)
Unknown	3 (0.6)
History of CCVD, n (%)	
No	256 (55.3)
Yes	207 (44.7)
History of dyslipidemia, n (%)	
No	266 (57.5)
Yes	188 (40.6)
Unknown	9 (1.9)
Mean baseline respiratory rate, breaths/min	17.7±1.9
Mean heart rate, beats/min	73.6±9.6
Mean SeSBP, mmHg	142.8±16.7
Abnormal SeSBP, n (%)	264 (57.0)
Mean SeDBP, mmHg	82.1±10.2
Abnormal SeDBP, n (%)	108 (23.3)
Hypertension severity, n (%)	
No	188 (40.6)
Mild	197 (42.5)
Moderate	67 (14.5)
Severe	11 (2.4)
History of hypertension treatment, n (%)	
Yes	446 (96.3)
No	17 (3.7)
History of antihypertensive drugs, n (%)	
Monotherapy	237 (51.2)
Double combination	164 (35.4)
Triple combination	37 (8.0)
Unknown	25 (5.4)
History of antihypertensive medication, n (%)	
Calcium channel blocker	281 (60.7)
Angiotensin II antagonist	338 (73.0)
Angiotensin-converting enzyme inhibitor	36 (7.8)
Combination, n (%)	
No combination	349 (75.4)
Lipid-modifying agent	33 (7.1)
Lipid-modifying agent and others[a]	81 (17.5)

[a]Any medications apart from antihypertensive agents and lipid-modifying agent. Data are presented as n (%), mean ± SD or median ± IQR. BMI, body mass index; CCVD, cardiovascular and cerebrovascular disease; SeSBP, seated systolic blood pressure; SeDBP, seated diastolic blood pressure.

Home-measured BP is reduced after OM-AML treatment. Home-measured SeSBP and SeDBP were significantly decreased from W1 to W8 (Fig. 3A). The mean changes of weekly home-measured SeSBP from W2 to W8 were -1.9, -2.4, -2.9, -3.8, -4.5, -4.8 and -5.0, respectively. Additionally, the mean changes of weekly home-measured SeDBP from W2 to W8 were -0.8, -1.2, -1.5, -1.7, -2.0, -2.3 and -2.1, respectively (Fig. 3B). The post hoc comparisons of home-measured BP are shown in Table SVI.

Satisfaction is improved and medication possession is high after OM-AML treatment. The satisfaction of both patients and physicians was significantly increased at W8 compared with W0 (Fig. 4A and B). MPR for W0-W4 and W0-W8 was 95.5 and 92.5%, respectively (Fig. 4C).

OM-AML treatment is generally tolerable. The most common AEs were nervous system disorder (13.4%), vascular disorder (9.7%), general disorder and administration site conditions (6.5%) and cardiac disorder (4.5%). Additionally, severe AEs (grade 3-4 AEs) included vascular disorder (0.6%), cardiac disorder (0.4%), respiratory, thoracic and mediastinal disorder (0.2%), general disorders and administration site conditions (0.2%), and reproductive system and breast disorders (0.2%).

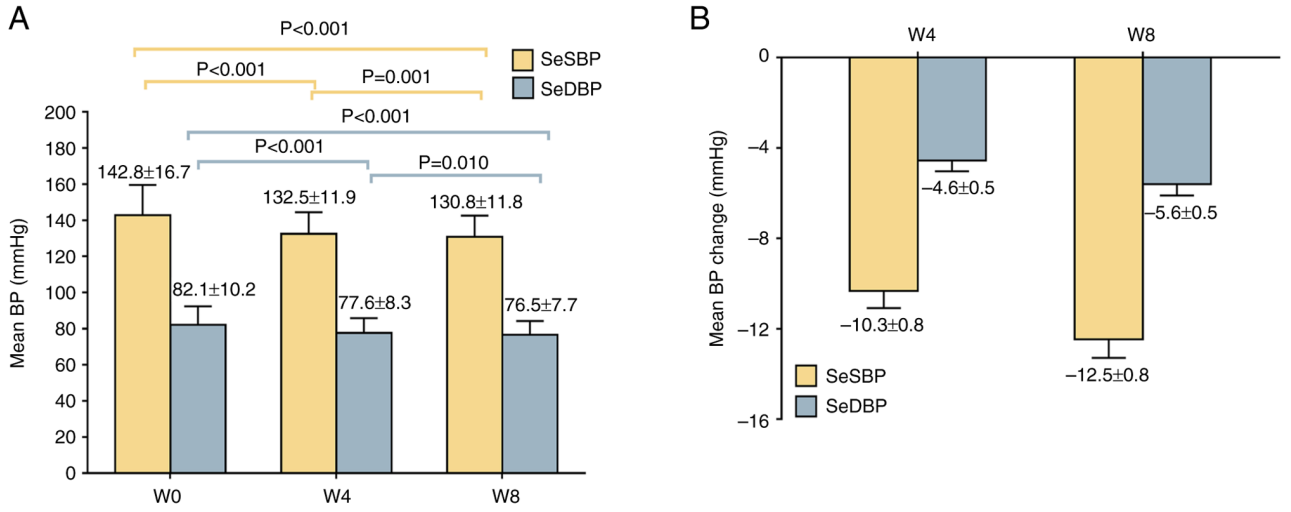

Figure 1. SeSBP and SeDBP following treatment. (A) SeSBP and SeDBP at W0, W4 and W8. (B) Changes in SeSBP and SeDBP at W4 and W8. Data are presented as mean ± SD. SeSBP, seated systolic blood pressure; SeDBP, seated diastolic blood pressure; W, week.

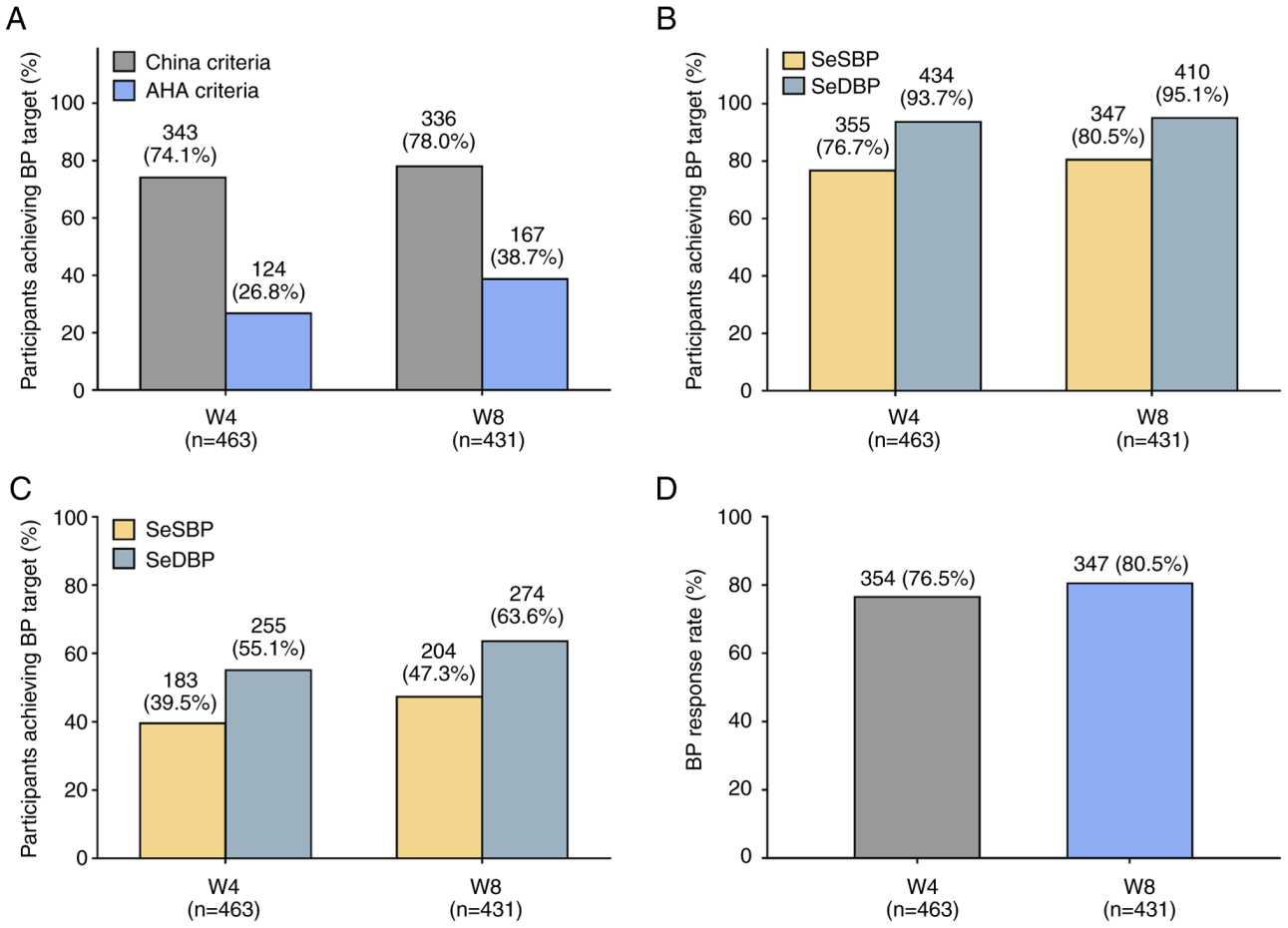

Figure 2. Achievement of BP target. (A) Proportion of patients who achieved BP target according to Chinese or AHA criteria at W4 and W8. Proportion of patients who achieved SeSBP or SeDBP targets according to (B) Chinese and (C) AHA criteria at W4 and W8. (D) BP response rate at W4 and W8. AHA, American Heart Association; W, week; SeSBP, seated systolic blood pressure; SeDBP, seated diastolic blood pressure.

Furthermore, the most common drug-associated AEs (AEs that were associated with the drug use, as evaluated by the investigators) were nervous system disorder (4.5%), vascular disorder (2.8%), and general disorder and administration site conditions (2.6%; Table III).

Discussion

OM-AML tablets are an effective antihypertensive agent not only for the general population, but also for older patients, and patients with diabetes mellitus or obesity (22,23).

Table II. Achievement of BP target rate and BP response rate at week 8 (n=431).

Characteristic	N	AHA BP target, n (%)	P-value	China BP target, n (%)	P-value	BP response, n (%)	P-value
Sex			0.002		0.096		0.069
Female	223	102 (45.7)		181 (81.2)		187 (83.9)	
Male	208	65 (31.3)		155 (74.5)		160 (76.9)	
BMI[a], kg/m^2			0.878		0.767		0.371
<30	394	152 (38.6)		306 (77.7)		315 (79.9)	
≥30	30	12 (40.0)		24 (80.0)		26 (86.7)	
Highest completed education level			0.306		0.515		0.530
Primary school or less	80	37 (46.3)		60 (75.0)		62 (77.5)	
High school	249	93 (37.3)		199 (79.9)		205 (82.3)	
Undergraduate or above	102	37 (36.3)		77 (75.5)		80 (78.4)	
Smoker			0.067		0.199		0.297
No	317	131 (41.3)		252 (79.5)		259 (81.7)	
Yes	114	36 (31.6)		84 (73.7)		88 (77.2)	
Alcohol intake			0.078		0.176		0.126
No	380	153 (40.3)		300 (78.9)		310 (81.6)	
Yes	51	14 (27.5)		36 (70.6)		37 (72.5)	
Time since hypertension diagnosis, years			0.016		0.307		0.668
<5	87	45 (51.7)		73 (83.9)		73 (83.9)	
5-9	55	22 (40.0)		43 (78.2)		44 (80.0)	
≥10	289	100 (34.6)		220 (76.1)		230 (79.6)	
Family history of hypertension			0.657		0.676		0.803
No	178	70 (39.3)		140 (78.7)		144 (80.9)	
Yes	234	87 (37.2)		180 (76.9)		187 (79.9)	
History of allergy			0.845		0.813		0.840
No	382	148 (38.7)		296 (77.5)		306 (80.1)	
Yes	43	16 (37.2)		34 (79.1)		35 (81.4)	
History of respiratory disease			0.436		0.556		0.565
No	386	147 (38.1)		299 (77.5)		309 (80.1)	
Yes	43	19 (44.2)		35 (81.4)		36 (83.7)	
History of kidney disease			0.210		0.701		0.451
No	402	153 (38.1)		314 (78.1)		325 (80.8)	
Yes	28	14 (50.0)		21 (75.0)		21 (75.0)	
History of diabetes			0.814		0.637		0.735
No	332	127 (38.3)		260 (78.3)		268 (80.7)	
Yes	96	38 (39.6)		73 (76.0)		76 (79.2)	
History of CCVD			0.596		0.713		0.923
No	234	88 (37.6)		184 (78.6)		188 (80.3)	
Yes	197	79 (40.1)		152 (77.2)		159 (80.7)	
History of dyslipidemia			0.743		0.060		0.105
No	245	98 (40.0)		200 (81.6)		205 (83.7)	
Yes	177	68 (38.4)		131 (74.0)		137 (77.4)	
Respiratory rate			1.000		1.000		1.000
Normal	356	146 (41.0)		283 (79.5)		294 (82.6)	
Abnormal	5	2 (40.0)		4 (80.0)		4 (80.0)	
Heart rate (%)			0.246		0.193		0.441
Normal	397	153 (38.5)		308 (77.6)		319 (80.4)	
Abnormal	26	13 (50.0)		23 (88.5)		23 (88.5)	

Table II. Continued.

Characteristic	N	AHA BP target, n (%)	P-value	China BP target, n (%)	P-value	BP response, n (%)	P-value
SeSBP			<0.001		<0.001		<0.001
Normal	180	90 (50.0)		162 (90.0)		168 (93.3)	
Abnormal	251	77 (30.7)		174 (69.3)		179 (71.3)	
SeDBP			0.001		0.034		0.017
Normal	330	142 (43.0)		265 (80.3)		274 (83.0)	
Abnormal	101	25 (24.8)		71 (70.3)		73 (72.3)	
Hypertension severity			0.950		0.097		0.034
Mild	189	57 (30.2)		138 (73.0)		143 (75.7)	
Moderate or severe	72	22 (30.6)		45 (62.5)		45 (62.5)	
History of hypertension treatment			0.420		0.774		0.754
Yes	414	162 (39.1)		323 (78.0)		334 (80.7)	
No	17	5 (29.4)		13 (76.5)		13 (76.5)	
History of antihypertensive drugs			0.566		0.005		0.070
Monotherapy	224	92 (41.1)		187 (83.5)		189 (84.4)	
Double combination	146	54 (37.0)		106 (72.6)		109 (74.7)	
Triple combination	36	12 (33.3)		23 (63.9)		29 (80.6)	
History of calcium channel blockers			0.192		0.814		0.209
No	64	30 (46.9)		53 (82.8)		56 (87.5)	
Yes	271	103 (38.0)		221 (81.5)		219 (80.8)	
History of angiotensin II antagonists			0.119		1.000		1.000
No	7	5 (71.4)		6 (85.7)		6 (85.7)	
Yes	328	128 (39.0)		268 (81.7)		269 (82.0)	
History of angiotensin-converting enzyme inhibitors			0.736		0.058		0.140
No	302	119 (39.4)		251 (83.1)		251 (83.1)	
Yes	33	14 (42.4)		23 (69.7)		24 (72.7)	
Combination			0.009		0.001		0.002
No combination	325	139 (42.8)		266 (81.8)		273 (84.0)	
Lipid-modifying agent	32	10 (31.3)		24 (75.0)		25 (78.1)	
Lipid-modifying agent and other	74	18 (24.3)		46 (62.2)		49 (66.2)	

[a]Seven patients had no BMI data, thus the comparison was made in 424 patients. AHA, American Heart Association; BMI, body mass index; CCVD, cardiovascular and cerebrovascular disease; SeSBP, seated systolic blood pressure; SeDBP, seated diastolic blood pressure.

Regarding the effect of OM-AML tablets on older patients with essential hypertension, a previous study demonstrated that the mean change of SeSBP/SeDBP was -14.5/-7.8 mmHg in older patients with uncontrolled hypertension who had previously received monotherapy followed by administration of OM-AML tablets for 20 weeks (24). Another study showed that after treatment with OM-AML tablets for 36 months, SeSBP/SeDBP decreased from 157.2/84.6 to 132.6/72.6 mmHg in older patients with hypertension (25), resulting in a mean change of -24.6/-12.0 mmHg for SeSBP/SeDBP. To the best of our knowledge, however, no similar studies have been performed in China. Due to differences in ethnicity, as well as lifestyle factors of Chinese patients, including high sodium and low potassium intake, low levels of physical exercise and high levels of alcohol abuse, evaluating the efficacy of OM-AML tablets in older patients with essential hypertension in China is of marked importance. The present study revealed that the mean change of SeSBP/SeDBP in older patients with essential hypertension was -12.5/-5.6 mmHg. The change of SeSBP/SeDBP was lower compared with that reported in previous studies (20 weeks and 36 months, respectively) (24,25). This may be due to the different duration of treatment, which was 8 weeks in the present study. However, OM-AML tablets could effectively lower BP in older patients with essential hypertension.

Decreasing BP to a particular threshold is the main objective of antihypertensive treatment. A previous study showed that 62.5% of older patients with resistant hypertension achieved the goal of SeSBP/SeDBP <140/90 mmHg following treatment with OM-AML tablets for 8 weeks (26) Additionally, a BP threshold of <140/90 mmHg was achieved

Table III. AEs by system organ class.

System organ class	Any AE, n (%)	Severe AE, n (%)	Drug-associated AE, n (%)
Nervous system disorder	62 (13.4)	0 (0.0)	21 (4.5)
Vascular disorder	45 (9.7)	3 (0.6)	13 (2.8)
General disorder and administration site conditions	30 (6.5)	1 (0.2)	12 (2.6)
Cardiac disorder	21 (4.5)	2 (0.4)	9 (1.9)
Gastrointestinal disorder	18 (3.9)	0 (0.0)	6 (1.3)
Respiratory, thoracic and mediastinal disorder	15 (3.2)	2 (0.4)	1 (0.2)
Metabolism and nutrition disorder	12 (2.6)	0 (0.0)	0 (0.0)
Psychiatric disorder	8 (1.7)	0 (0.0)	6 (1.3)
Skin and subcutaneous tissue disorder	7 (1.5)	0 (0.0)	2 (0.4)
Musculoskeletal and connective tissue disorder	7 (1.5)	0 (0.0)	0 (0.0)
Investigations	4 (0.9)	0 (0.0)	0 (0.0)
Eye disorder	3 (0.6)	0 (0.0)	1 (0.2)
Reproductive system and breast disorder	3 (0.6)	1 (0.2)	0 (0.0)
Renal and urinary disorder	3 (0.6)	0 (0.0)	0 (0.0)
Endocrine disorder	2 (0.4)	0 (0.0)	0 (0.0)
Immune system disorder	1 (0.2)	0 (0.0)	1 (0.2)
Hepatobiliary disorder	1 (0.2)	0 (0.0)	0 (0.0)

AE, adverse event.

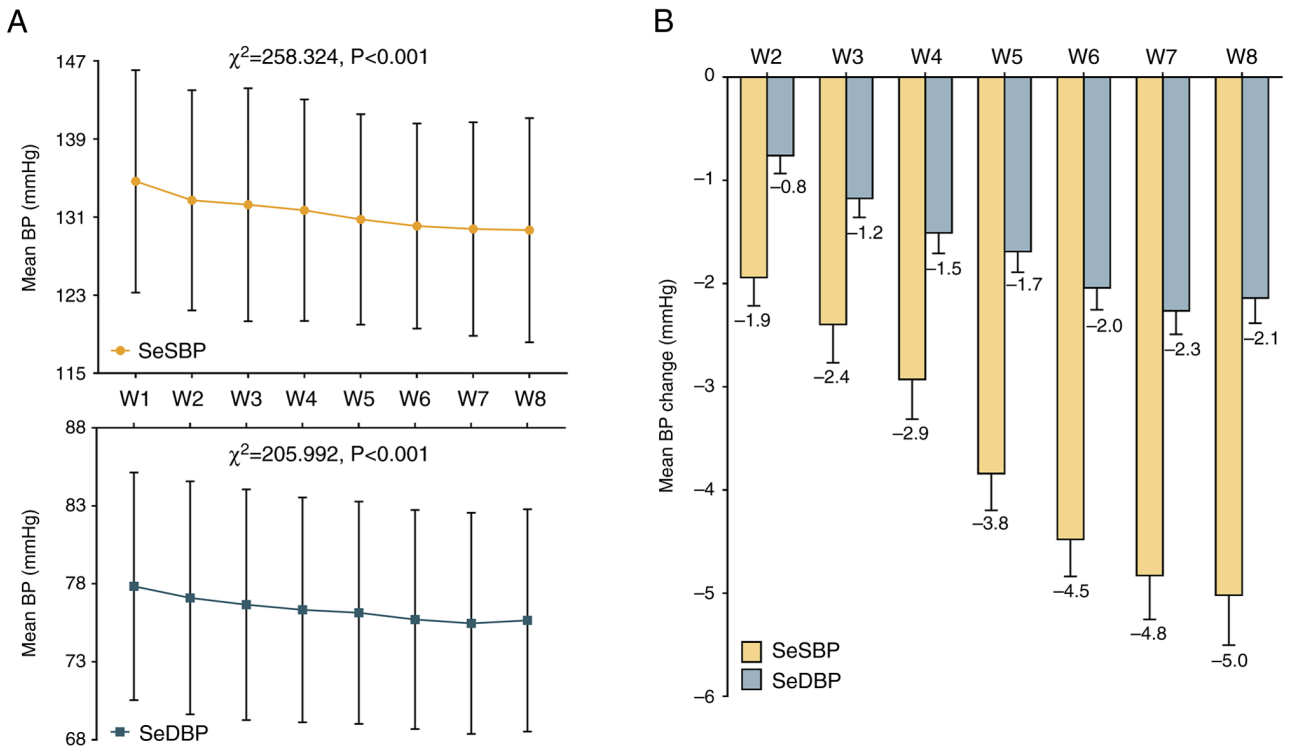

Figure 3. Home-measured BP following treatment. (A) Home-measured SeSBP and SeDBP from W1 to W8. Data are presented as mean ± SD. (B) Changes in home-measured SeSBP and SeDBP from W2 to W8. Data are presented as mean ± SEM. W, week; SeSBP, seated systolic blood pressure; SeDBP, seated diastolic blood pressure.

by 86.8% of older patients with essential hypertension receiving OM-AML tablets for 20 weeks (24). Furthermore, another study reported that 51.4% of older patients with essential hypertension achieved a BP goal of <140/90 mmHg after treatment with OM-AML tablets for 10 weeks (27). In the present study, 78.0 and 38.7% of older patients achieved a BP target of <140/90 and <130/80 mmHg, based on the China and AHA criteria, respectively. The aforementioned results

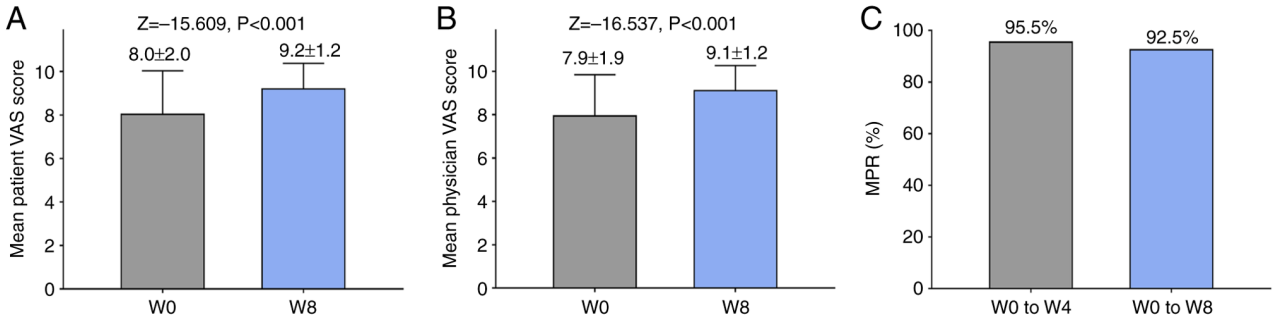

Figure 4. Satisfaction and MPR following treatment. The satisfaction of (A) patients and (B) physicians at W0 and W8 was evaluated. (C) MPR at W4 and W8 was determined. W, week; MPR, medication possession rate; VAS, visual analogue scale.

were consistent with those reported in previous studies, which used a BP goal of <140/90 mmHg (24,26,27). Additionally, compared with previous studies on older patients with hypertension treated with OM or AML monotherapy (22,28), the present study revealed that a higher proportion of patients achieved a BP target of <140/90 mmHg. This could be due to the fact that OM-AML tablets combine two antihypertensive drugs with high efficacy, thus displaying superior treatment efficacy.

During the treatment of essential hypertension, both patient and physician satisfaction should be considered. Satisfaction is commonly associated with treatment efficacy, convenience of treatment and cost (8,9,18). Consistent with a previous study (29), satisfaction of both patients and physicians in the present study was increased at W8 compared with at W0. This may be because OM-AML tablets were effective in controlling BP, thus enhancing both patient and physician satisfaction and OM-AML tablets were convenient to take due to their single-pill, dose-fixed design, reducing the probability of missing doses, thus also increasing the satisfaction of both patients and physicians. Additionally, the present study reported a MPR of 92.5% at W8, which was similar to that reported in Korean patients with essential hypertension treated with a dose-fixed OM/AML/hydrochlorothiazide regimen (29).

Due to comorbidities and frailty, the safety of antihypertensive drugs is a key issue during the treatment of older patients with essential hypertension (3,5). The present study revealed that the incidence of OM-AML-associated AEs in older patients with essential hypertension was similar to that reported in previous studies (24-27). In addition, the incidence of severe AEs was relatively low, indicating that OM-AML tablets could be considered a safe antihypertensive drug.

The present study had some limitations. Firstly, the present study was a prospective, observational, single-cohort study that evaluated the efficacy and safety of OM-AML tablets in older patients with essential hypertension. However, further randomized, controlled trials should be performed to provide more evidence for the administration of OM-AML tablets in these patients. Secondly, a 10-cm VAS scale was used to assess the satisfaction of both patients and physicians. This scale is characterized by ease of assessment; however, this leads to an increased risk of bias. Thirdly, the long-term efficacy and safety of OM-AML tablets in older patients with essential hypertension should be further explored in the future.

In conclusion, the present study indicated that OM-AML tablets were an effective and safe antihypertensive drug, facilitating the achievement of BP targets in older patients with essential hypertension.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JG, ZC and JD contributed to conception and design of study. ZC, ZQ, WH, GM, YL, RW, LC, LF, MH, YH, MW, JX, YX, ZW, XJ, JH, DF, LT, WC, XCa, YJ, YZ, LH, PB, XCh, PD, XH, MLL, XW, KH, YLL, YWL, DL, JuW, JiW, GF, LW and MQL were responsible for acquisition of data. JG, ZC, ZQ, WC, WH, GM, JD, LW and ML performed data analysis and interpreted data. JG and ZC confirm the authenticity of all the raw data. JG, ZC, JD, LW and ML drafted the manuscript and all other authors provided critical revision. All authors read and approved the final version of manuscript.

Ethics approval and consent to participate

A detailed description of the SVK study design is available in Chinese Clinical Trial Registry (chictr.org.cn/; registration no. ChiCTR1900026574). The present study was approved by the Ethics Committee of Zhongshan Hospital, Fudan University (approval no. B2019-174R2; Shanghai, China). All patients provided written informed consent.

Patient consent for publication

Not applicable.

Competing interests

JD, LW and MLi are employees of Daiichi Sankyo (China) Holdings Co., Ltd., the company that makes SVK. The other authors declare that they have no competing interests.

References

1. Zhou B, Perel P, Mensah GA and Ezzati M: Global epidemiology, health burden and effective interventions for elevated blood pressure and hypertension. Nat Rev Cardiol 18: 785-802, 2021.
2. Boutouyrie P, Chowienczyk P, Humphrey JD and Mitchell GF: Arterial stiffness and cardiovascular risk in hypertension. Circ Res 128: 864-886, 2021.
3. Oliveros E, Patel H, Kyung S, Fugar S, Goldberg A, Madan N and Williams KA: Hypertension in older adults: Assessment, management, and challenges. Clin Cardiol 43: 99-107, 2020.
4. Benetos A, Petrovic M and Strandberg T: Hypertension management in older and frail older patients. Circ Res 124: 1045-1060, 2019.
5. Yasuda S, Miyamoto Y and Ogawa H: Current status of cardiovascular medicine in the aging society of Japan. Circulation 138: 965-967, 2018.
6. Mohsen Ibrahim M: Hypertension in developing countries: A major challenge for the future. Curr Hypertens Rep 20: 38, 2018.
7. Mills KT, Stefanescu A and He J: The global epidemiology of hypertension. Nat Rev Nephrol 16: 223-237, 2020.
8. Thomas NF and Dunn KS: Self-transcendence and medication adherence in older adults with hypertension. J Holist Nurs 32: 316-326, 2014.
9. Lo SH, Chau JP, Woo J, Thompson DR and Choi KC: Adherence to antihypertensive medication in older adults with hypertension. J Cardiovasc Nurs 31: 296-303, 2016.
10. Erdine S: Olmesartan/amlodipine: Blood pressure lowering and beyond in special populations. Ther Adv Cardiovasc Dis 6: 31-44, 2012.
11. Zhang X, Zhang H, Ma Y, Che W and Hamblin MR: Management of hypertension using olmesartan alone or in combination. Cardiol Ther 6: 13-32, 2017.
12. Parati G, Kjeldsen S, Coca A, Cushman WC and Wang J: Adherence to Single-Pill versus free-equivalent combination therapy in hypertension: A systematic review and meta-analysis. Hypertension 77: 692-705, 2021.
13. Al-Makki A, DiPette D, Whelton PK, Murad MH, Mustafa RA, Acharya S, Beheiry HM, Champagne B, Connell K, Cooney MT, *et al*: Hypertension pharmacological treatment in adults: A World Health organization guideline executive summary. Hypertension 79: 293-301, 2022.
14. Bakris G, Ali W and Parati G: ACC/AHA Versus ESC/ESH on hypertension guidelines: JACC guideline comparison. J Am Coll Cardiol 73: 3018-3026, 2019.
15. Derosa G, Mugellini A, Pesce RM, D'Angelo A and Maffioli P: Olmesartan combined with amlodipine on oxidative stress parameters in type 2 diabetics, compared with single therapies: A randomized, controlled, clinical trial. Medicine (Baltimore) 95: e3084, 2016.
16. Chrysant SG, Melino M, Karki S, Lee J and Heyrman R: The combination of olmesartan medoxomil and amlodipine besylate in controlling high blood pressure: COACH, a randomized, double-blind, placebo-controlled, 8-week factorial efficacy and safety study. Clin Ther 30: 587-604, 2008.
17. Volpe M, Brommer P, Haag U and Miele C: Efficacy and tolerability of olmesartan medoxomil combined with amlodipine in patients with moderate to severe hypertension after amlodipine monotherapy: A randomized, double-blind, parallel-group, multicentre study. Clin Drug Investig 29: 11-25, 2009.
18. Levi M, Pasqua A, Cricelli I, Cricelli C, Piccinni C, Parretti D and Lapi F: Patient adherence to olmesartan/amlodipine combinations: Fixed versus extemporaneous combinations. J Manag Care Spec Pharm 22: 255-262, 2016.
19. Lucas C, Romatet S, Mekiès C, Allaf B and Lantéri-Minet M: Stability, responsiveness, and reproducibility of a visual analog scale for treatment satisfaction in migraine. Headache 52: 1005-1018, 2012.
20. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, *et al*: 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 71: e13-e115, 2018.
21. Wu S, Xu Y, Zheng R, Lu J, Li M, Chen L, Huo Y, Xu M, Wang T, Zhao Z, *et al*: Hypertension Defined by 2017 ACC/AHA guideline, ideal cardiovascular health metrics, and risk of cardiovascular disease: A nationwide prospective cohort study. Lancet Reg Health West Pac 20: 100350, 2022.
22. Chrysant SG, Lee J, Melino M, Karki S and Heyrman R: Efficacy and tolerability of amlodipine plus olmesartan medoxomil in patients with difficult-to-treat hypertension. J Hum Hypertens 24: 730-738, 2010.
23. Oparil S, Lee J, Karki S and Melino M: Subgroup analyses of an efficacy and safety study of concomitant administration of amlodipine besylate and olmesartan medoxomil: Evaluation by baseline hypertension stage and prior antihypertensive medication use. J Cardiovasc Pharmacol 54: 427-436, 2009.
24. Weir MR, Shojaee A and Maa JF: Efficacy of amlodipine/olmesartan medoxomil +/- hydrochlorothiazide in patients aged >/=65 or <65 years with uncontrolled hypertension on prior monotherapy. Postgrad Med 125: 124-134, 2013.
25. Ogawa H, Kim-Mitsuyama S, Matsui K, Jinnouchi T, Jinnouchi H and Arakawa K; OlmeSartan and Calcium Antagonists Randomized (OSCAR) Study Group: Angiotensin II receptor blocker-based therapy in Japanese elderly, high-risk, hypertensive patients. Am J Med 125: 981-990, 2012.
26. Ding S, Liu J, Fu Q and Zheng Y: Clinical effects of combined olmesartan medoxomil and amlodipine on clinic and ambulatory blood pressure in elderly patients with resistant hypertension. Arch Gerontol Geriatr 57: 423-427, 2013.
27. Kreutz R, Ammentorp B, Laeis P and de la Sierra A: Efficacy and tolerability of triple-combination therapy with olmesartan, amlodipine, and hydrochlorothiazide: A subgroup analysis of patients stratified by hypertension severity, age, sex, and obesity. J Clin Hypertens (Greenwich) 16: 729-740, 2014.
28. Zhu JR, Zhang SY and Gao PJ: Efficacy and safety of olmesartan medoxomil/amlodipine fixed-dose combination for hypertensive patients uncontrolled with monotherapy. Arch Pharm Res 37: 1588-1598, 2014.
29. Sohn IS, Ihm SH, Kim GH, Park SM, Hong BK, Lee CH, Lee SH, Chang DI, Joo SP, Lee SC, *et al*: Real-world evidence on the strategy of olmesartan-based triple single-pill combination in Korean hypertensive patients: A prospective, multicenter, observational study (RESOLVE-PRO). Clin Hypertens 27: 21, 2021.