



# Single-Pill Combination Olmesartan/Amlodipine/Hydrochlorothiazide Safety and Effectiveness in Older Patients with Hypertension: Pooled Analysis of Post-Approval Observational Studies

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## ABSTRACT

**Introduction:** Despite needing intensive blood pressure (BP) control, elderly patients with hypertension may be undertreated because of concern about potential hypotension-related adverse events (AEs). Many older patients need combination therapy to achieve BP targets. This study investigated whether single-pill

combination (SPC) antihypertensive therapy may benefit such patients.

**Methods:** This study analyzed pooled data from patients treated with olmesartan/amlodipine/hydrochlorothiazide (O/A/H) SPC therapy in three multicenter, prospective, observational studies (RESOLVE, RESOLVE-PRO and RESOLVE-INT) in South Korea. The primary endpoint was the incidence of hypotension-related AEs (hypotension/orthostatic hypotension, dizziness/postural dizziness, syncope, falls/fractures), stratified by age: <65 years (non-elderly), 65–79 years (elderly), and ≥80 years (very elderly). Secondary endpoints included hypotension-related AEs stratified by O/A/H dose and by baseline systolic BP (SBP) and diastolic BP (DBP), and SBP change from baseline to Week 24, and at Weeks 8, 16 and 24, stratified by age.

**Results:** From 16,646 pooled participants, 10,948 met the inclusion criteria and received ≥1 dose of O/A/H (safety set): 5892 were <65 years old, 4143 were 65–79, and 911 were aged ≥80 years (two had missing age data). The effectiveness set comprised 9292 with complete BP data. Hypotension-related AEs occurred in 4.82% (95% CI 4.29, 5.40) of non-elderly patients, 4.44% (95% CI 3.83, 5.11) of elderly patients, and 4.61% (95% CI 3.34, 6.18) of the very elderly group, with no statistically significant difference in relative risk between age groups. There was no difference in relative risk of hypotension-related AEs with increased O/A/H dosage

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in patients aged >65 years and stratified by baseline SBP or DBP. All groups achieved effective BP reductions, with mean BP <140/90 mmHg at 24 weeks.

**Conclusion:** The O/A/H single-pill combination is well tolerated and effective in elderly and very elderly Korean patients with hypertension, offering a safe and practical therapeutic option for achieving BP control in the aging hypertensive population.

**Trial Registration:** Clinical Research Information Service—Republic of Korea, KCT0010343 ([https://cris.nih.go.kr/cris/search/detailSearch.do?seq=29557&search\\_page=L](https://cris.nih.go.kr/cris/search/detailSearch.do?seq=29557&search_page=L)).

**Keywords:** Hypertension; Hypotension-related adverse events; Olmesartan; Amlodipine; Hydrochlorothiazide; Real-world; Effective blood pressure control; Single-pill combination; Safety; Korea

### Key Summary Points

#### *Why carry out this study?*

Controlling hypertension in older patients often requires multi-drug therapy, and hypotension is a potential clinical concern.

Olmesartan + amlodipine + hydrochlorothiazide (O/A/H) is an effective and commonly used combination antihypertensive, but real-world data on its use in older patients are limited.

We compared hypotension-related adverse event rates and blood pressure changes among patients aged <65, ≥65, and ≥85 years who received O/A/H treatment for 24 weeks.

#### *What was learned from the study?*

Approximately 4–5% of patients had hypotension-related adverse events, with no significant differences by age or O/A/H dose, and the mean blood pressure was reduced to <140/90 mmHg across all age groups.

O/A/H antihypertensive therapy was effective, with no excess risk of hypotension-related adverse events in elderly or very elderly patients, even at higher doses, suggesting that concerns about hypotension should not preclude appropriate treatment to control blood pressure in older patients.

O/A/H offers a practical, well tolerated, and effective option for achieving recommended blood pressure targets in the aging hypertensive population.

## INTRODUCTION

Hypertension is a significant risk factor for cardiovascular diseases (CVD) and is the leading preventable cause of CVD mortality [1, 2]. Effective management of hypertension is critical to reducing this substantial disease burden. International guidelines, including those from the European Society of Cardiology (ESC), European Society of Hypertension (ESH), and American College of Cardiology/American Heart Association, recommend intensive blood pressure (BP) control strategies to optimize cardiovascular (CV) outcomes, particularly in older people [2–5].

Antihypertensive therapy to control BP in older patients is generally well tolerated and significantly reduces CV morbidity and mortality [6, 7]. Although hypertension guidelines vary internationally, the current European, Republic of Korea, and Taiwan guidelines are aligned, with a target systolic BP (SBP) of <140 mmHg for patients aged ≥65 years [2, 3, 8]. These recommendations are supported by large randomized controlled trials (RCTs), such as the Systolic Blood Pressure Intervention Trial (SPRINT) and the Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients (STEP) trial, which demonstrated that intensive BP lowering in elderly patients significantly reduced CV events and mortality, without compromising safety [9, 10].

Nevertheless, concerns regarding hypotension-related adverse events (AEs), such as dizziness, syncope, and falls, often persist among

clinicians, potentially leading to therapeutic inertia and undertreatment in older patients despite the clear benefits of intensive BP management demonstrated in landmark trials [9–14]. In clinical practice, many older patients require combination antihypertensive therapy to achieve BP targets, with a fixed-dose single-pill combination (SPC) commonly prescribed [2, 3]. In South Korea, 18% of patients aged  $\geq 65$  years are prescribed combination therapy with three or more antihypertensive agents [15]. The fixed-dose SPC of olmesartan, amlodipine, and hydrochlorothiazide (O/A/H) is commonly used, and its safety and antihypertensive efficacy have been well documented in RCTs and post-marketing studies [11, 16, 17]. Importantly, the O/A/H combination was prominently utilized in the STEP trial, further validating its clinical efficacy and safety profile [10].

Given the limited data specifically evaluating older and very elderly people with hypertension in routine clinical settings, we conducted a pooled analysis of three earlier prospective observational studies [18–20] to comprehensively assess the safety and effectiveness of the O/A/H SPC in elderly (65–79 years) and very elderly ( $\geq 80$  years) patients. This study focused on examining the incidence of hypotension-related AEs and BP reduction outcomes across different age and dosage groups.

## METHODS

### Study Data, Design, and Population

Data were pooled from three multicenter observational studies, two prospective (RESOLVE, RESOLVE-PRO) and one retrospective (RESOLVE-INT), which were conducted in South Korea between 2015 and 2020 to evaluate antihypertensive treatment with the O/A/H SPC (Sevikar HCT®, Daiichi Sankyo Korea Co., Seoul, Republic of Korea) [18–20]. The original studies analyzed data collected during outpatient visits as part of routine clinical care at participating study sites in South Korea; BP measurements were obtained using standard sphygmomanometers, and occurrences of reported AEs were recorded

at each visit. Table S1 (Supplemental Appendix) summarizes the characteristics of the three studies. This study was approved by the Institutional Review Board of Asan Medical Center, Seoul, Republic of Korea (IRB no. 2024-0503).

The RESOLVE, RESOLVE-PRO, and RESOLVE-INT studies enrolled 16,646 patients, of whom this pooled analysis included only those who met the eligibility criteria defined in the respective RESOLVE study protocols [18–20]. Additionally, it excluded patients whose SBP or diastolic BP (DBP) was not measured at baseline or who had outlier BP values, those whose BP was controlled at baseline (i.e., SBP < 140 mmHg and DBP < 90 mmHg), and those who did not receive O/A/H (Fig. 1).

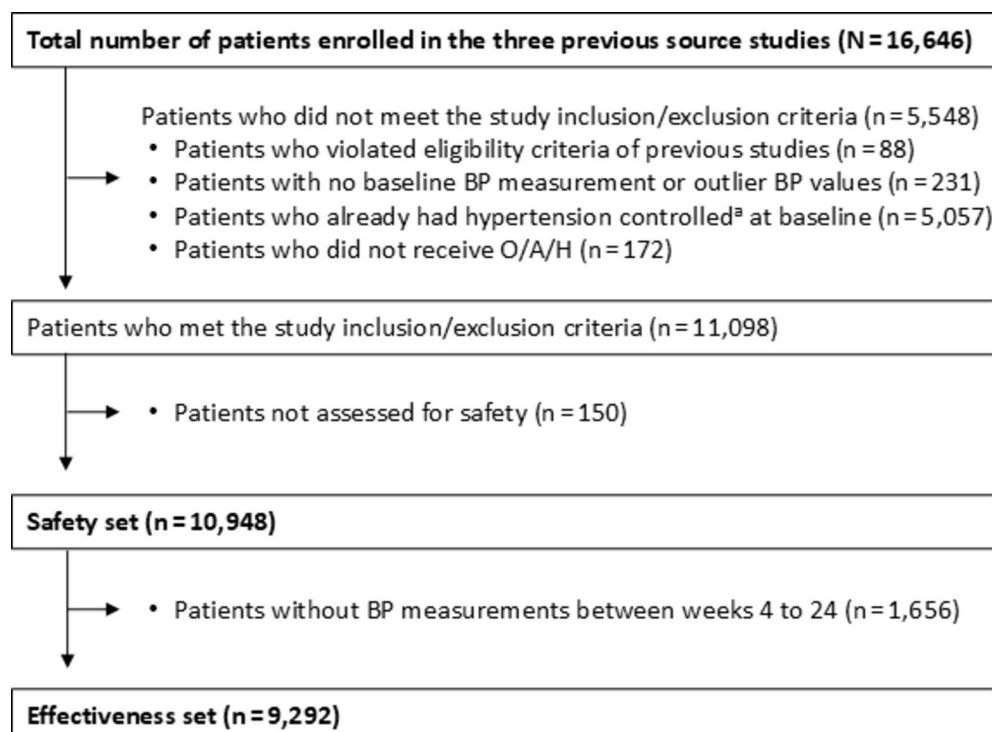
The study population was stratified into three age groups for the primary endpoint analysis: < 65 years (non-elderly), 65–79 years (elderly), and  $\geq 80$  years (very elderly), following the classification used in the Korea Hypertension Fact Sheets for 2022 (elderly) [21] and 2023 (special populations) [22]. Some endpoints were also analyzed in two age groups, < 65 (non-elderly) and  $\geq 65$  (geriatric) years. Age-stratified analyses excluded two patients from the safety set and one from the effectiveness set whose age data were missing.

### Ethical Approval

The study protocol was approved by the Institutional Review Board of Asan Medical Center, Seoul, Republic of Korea (IRB no. 2024-0503) and was conducted in accordance with the principles of the Declaration of Helsinki 1964 and its later amendments, as well as the rules of the IRB. All patients voluntarily provided written informed consent before enrolling in the study. Study data were de-identified to protect the privacy of the participating patients and to comply with locally applicable regulations.

### Safety and Efficacy Endpoints

The primary endpoint was the incidence of hypotension-related adverse events (AEs), stratified by age. Hypotension-related AEs were pre-defined as composite instances of hypotension



**Fig. 1** Patient disposition. <sup>a</sup>Systolic BP < 140 mmHg and diastolic BP < 90 mmHg. BP blood pressure, O/A/H olmesartan medoxomil/amlodipine besylate/hydrochlorothiazide

or orthostatic hypotension, dizziness or postural dizziness, syncope, fall, or fracture; and/or SBP < 90 mmHg during the study period; and/or discontinuation due to hypotension [10, 23–25]. The secondary endpoints for safety were the incidence of hypotension-related AEs, stratified by age, O/A/H dose, prior antihypertensive medication, and achieved target BPs.

The effectiveness endpoints were changes in BP from baseline at Weeks 8, 16, and 24, stratified by age, and changes at Week 24 stratified by the O/A/H dose and prior antihypertensive medication. In addition, a post hoc sensitivity analysis of BP change at Week 24 by O/A/H dose among patients who did not use concomitant antihypertensive medications was conducted.

### Statistical Analysis

Statistical analyses were conducted on the full analysis set using all available data, without imputation of missing data. To address potential

heterogeneity arising from the different source study designs (prospective and retrospective), raw data were harmonized using common definitions and coding rules prior to pooling. All analyses were conducted using Statistical Analysis Software, version 9.4 (SAS Institute Inc, Cary, NC, USA).

Comparisons of categorical data used Fisher's exact test instead of the chi-squared test if  $\geq 20\%$  of all cells had an expected frequency of < 5. If the assumption of normality was not satisfied based on the Kolmogorov-Smirnov test, non-parametric tests were used: the Kruskal-Wallis test was conducted instead of one-way ANOVA, the Wilcoxon rank-sum test was used instead of two-sample *t*-tests, and the Wilcoxon signed-rank test was used instead of paired *t*-tests. The Clopper-Pearson exact method was used to calculate the 95% confidence intervals (CI) for incidence of hypotension-related adverse events. Analysis of covariance (ANCOVA) was used to calculate *p*-values for BP changes from baseline to Week 24.

Determinants of systolic BP (SBP) change at Week 24 were identified by performing multi-variable linear regression analyses. The dependent variable was defined as the absolute change in SBP from baseline to Week 24. Independent variables included O/A/H dosage group (categorical), age, sex, body mass index (BMI), alcohol consumption, diabetes mellitus, CVD, presence of any CV risk factor, number of prior antihypertensive agents, and use of specific drug classes prior to enrollment (e.g., angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, calcium channel blockers, thiazide diuretics, loop diuretics, mineralocorticoid receptor antagonists, beta-blockers, and alpha-blockers). To address potential confounding by concomitant medications, the sensitivity analysis excluded patients who used other antihypertensive drugs (ATC codes C03, C07, C08, C09) together with O/A/H during the 24-week observation period. Variables were selected based on clinical relevance and availability across datasets. A  $p$ -value  $< 0.05$  was considered statistically significant in all models.

## RESULTS

### Study Population

From 16,646 participants enrolled in the RESOLVE, RESOLVE-PRO, and RESOLVE-INT studies [18–20], the safety set comprised 10,948 patients who received at least one dose of O/A/H SPC therapy and had been assessed for safety endpoints (Fig. 1). The effectiveness set included 9292 patients with complete BP data.

Table 1 summarizes the demographic parameters and clinical characteristics of the safety set. The mean ages of the non-elderly, elderly, and very elderly groups were  $51.68 \pm 9.41$ ,  $71.93 \pm 4.18$ , and  $83.11 \pm 3.01$  years, respectively. The proportion of women was lowest in the non-elderly group (33.38%) and highest in the very elderly group (70.47%). The percentage of smokers and alcohol consumers was highest in the non-elderly group and lowest in the very elderly group (Table 1). The prevalence of CVD

was highest in the very elderly group (40.18%) and lowest in the non-elderly group (21.47%).

Baseline DBP was significantly lower in elderly ( $85.20 \pm 11.34$  mmHg) and very elderly patients ( $82.98 \pm 12.62$  mmHg) than in non-elderly patients ( $93.08 \pm 11.48$  mmHg). Accordingly, pulse pressure was significantly higher in elderly ( $69.47 \pm 13.75$  mmHg) and very elderly patients ( $73.86 \pm 15.35$  mmHg) than in non-elderly patients ( $60.61 \pm 12.93$  mmHg) (Table 1). Previous antihypertensive drug use, defined by the number of different antihypertensive agents used prior to enrollment, differed significantly across the age groups ( $p < 0.0001$ ), with a higher proportion of non-elderly patients taking two or fewer drugs and proportionally more elderly or very elderly patients taking three or more (Table 1).

The corresponding data for the effectiveness set are shown in Table S2. The baseline characteristics within each age group were similar to those in the safety set.

At baseline, patients in the higher O/A/H dose groups (particularly O/A/H 10/40/12.5 mg) had more severe clinical conditions, including higher BMI (mean  $26.84$  vs.  $25.67$  kg/m<sup>2</sup>), greater prevalence of diabetes (36.42% vs. 29.54%), and CVD (30.41% vs. 25.69%) compared with the O/A/H 5/20/12.5 mg group (Table S3). They also had higher baseline SBP and more frequent prior use of multiple antihypertensive drug classes including angiotensin II receptor blockers, calcium channel blockers, thiazides, and beta-blockers (Table S3). Analysis of baseline characteristics stratified by the number of prior antihypertensive medications (Table S4) showed that treatment-naïve patients (0 prior drugs) had significantly higher baseline SBP than those previously treated with two or more agents ( $156.32 \pm 14.17$  vs.  $\geq 152.75 \pm 12.15$  mmHg,  $p < 0.0001$ ).

### Safety Outcomes

Hypotension-related AEs occurred in 4.82% (95% CI 4.29, 5.40), 4.44% (95% CI 3.83, 5.11), and 4.61% (95% CI 3.34, 6.18) of patients in the non-elderly, elderly, and very elderly groups, respectively, with no statistically significant differences among the three age groups (Table 2).

**Table 1** Baseline characteristics of safety set ( $N = 10,946^a$ ), by age group

| Continuous variables described as mean $\pm$ standard deviation; categorical variables described as frequency (percent) <sup>b</sup> | Non-elderly (< 65 years) ( $N = 5892$ ) | Elderly (65–79 years) ( $N = 4143$ ) | Very elderly ( $\geq 80$ years) ( $N = 911$ ) | Global $p$ -value <sup>c</sup> |
|--------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|--------------------------------------|-----------------------------------------------|--------------------------------|
| Patient demographics and health status                                                                                               |                                         |                                      |                                               |                                |
| Age (years)                                                                                                                          | 51.68 $\pm$ 9.41                        | 71.93 $\pm$ 4.18                     | 83.11 $\pm$ 3.01                              | < 0.0001 <sup>d</sup>          |
| Sex (female)                                                                                                                         | 1967 (33.38)                            | 2,245 (54.19)                        | 642 (70.47)                                   | < 0.0001 <sup>c</sup>          |
| Body mass index (kg/m <sup>2</sup> )                                                                                                 | 26.71 $\pm$ 4.29                        | 25.31 $\pm$ 3.48                     | 24.47 $\pm$ 3.50                              | < 0.0001 <sup>d</sup>          |
| Body mass index category (kg/m <sup>2</sup> )                                                                                        |                                         |                                      |                                               | < 0.0001 <sup>c</sup>          |
| < 23.0                                                                                                                               | 748 (16.50)                             | 767 (24.68)                          | 227 (33.83)                                   |                                |
| 23.0–24.9                                                                                                                            | 900 (19.85)                             | 810 (26.06)                          | 168 (25.04)                                   |                                |
| $\geq 25.0$                                                                                                                          | 2886 (63.65)                            | 1531 (49.26)                         | 276 (41.13)                                   |                                |
| Smoking (ever)                                                                                                                       | 1839 (38.74)                            | 632 (19.30)                          | 73 (9.97)                                     | < 0.0001 <sup>c</sup>          |
| Alcohol consumption                                                                                                                  | 2402 (55.72)                            | 923 (31.39)                          | 120 (18.32)                                   | < 0.0001 <sup>c</sup>          |
| Cardiovascular diseases                                                                                                              | 1265 (21.47)                            | 1355 (32.71)                         | 366 (40.18)                                   | < 0.0001 <sup>c</sup>          |
| Diabetes mellitus                                                                                                                    | 1598 (27.33)                            | 1509 (36.61)                         | 301 (33.19)                                   | < 0.0001 <sup>c</sup>          |
| Chronic kidney disease                                                                                                               | 141 (2.41)                              | 149 (3.61)                           | 47 (5.18)                                     | < 0.0001 <sup>c</sup>          |
| Stroke                                                                                                                               | 936 (15.89)                             | 828 (19.99)                          | 184 (20.20)                                   | 0.0002 <sup>c</sup>            |
| Coronary artery disease                                                                                                              | 567 (9.62)                              | 730 (17.62)                          | 160 (17.56)                                   | < 0.0001 <sup>c</sup>          |
| Cardiovascular risk factors                                                                                                          | 3815 (65.16)                            | 2796 (67.81)                         | 593 (65.38)                                   | 0.0191 <sup>c</sup>            |
| <i>Blood pressure, mmHg</i>                                                                                                          |                                         |                                      |                                               |                                |
| Systolic                                                                                                                             | 153.70 $\pm$ 13.48                      | 154.67 $\pm$ 12.60                   | 156.84 $\pm$ 13.53                            | < 0.0001 <sup>d</sup>          |
| Diastolic                                                                                                                            | 93.08 $\pm$ 11.48                       | 85.20 $\pm$ 11.34                    | 82.98 $\pm$ 12.62                             | < 0.0001 <sup>d</sup>          |
| Pulse pressure                                                                                                                       | 60.61 $\pm$ 12.93                       | 69.47 $\pm$ 13.75                    | 73.86 $\pm$ 15.35                             | < 0.0001 <sup>d</sup>          |
| Serum biochemistry test results                                                                                                      |                                         |                                      |                                               |                                |
| Creatinine (mg/dl), $n$                                                                                                              | 0.98 $\pm$ 0.96, 931                    | 1.31 $\pm$ 6.08, 549                 | 1.01 $\pm$ 0.55, 105                          | 0.0010 <sup>d</sup>            |
| Blood urea nitrogen (mg/dl), $n$                                                                                                     | 14.94 $\pm$ 7.94, 884                   | 17.47 $\pm$ 9.40, 516                | 18.32 $\pm$ 7.93, 105                         | < 0.0001 <sup>d</sup>          |
| Alanine aminotransferase (IU/l), $n$                                                                                                 | 32.40 $\pm$ 23.51, 926                  | 23.65 $\pm$ 16.24, 505               | 23.29 $\pm$ 31.90, 99                         | < 0.0001 <sup>d</sup>          |
| Aspartate aminotransferase (IU/l), $n$                                                                                               | 29.46 $\pm$ 16.79, 930                  | 25.87 $\pm$ 13.68, 509               | 28.39 $\pm$ 39.63, 102                        | < 0.0001 <sup>d</sup>          |
| Alkaline phosphatase (IU/l), $n$                                                                                                     | 107.45 $\pm$ 95.38, 670                 | 103.93 $\pm$ 75.84, 379              | 104.82 $\pm$ 100.06, 83                       | 0.5664 <sup>d</sup>            |
| Total bilirubin (mg/dl), $n$                                                                                                         | 0.78 $\pm$ 0.82, 732                    | 0.67 $\pm$ 0.30, 406                 | 0.70 $\pm$ 0.31, 88                           | < 0.0001 <sup>d</sup>          |
| Albumin (g/dl), $n$                                                                                                                  | 4.27 $\pm$ 0.44, 759                    | 4.11 $\pm$ 0.42, 427                 | 4.00 $\pm$ 0.52, 95                           | < 0.0001 <sup>d</sup>          |
| Total protein (g/dl), $n$                                                                                                            | 7.16 $\pm$ 0.61, 739                    | 7.04 $\pm$ 0.59, 402                 | 6.82 $\pm$ 1.01, 93                           | < 0.0001 <sup>d</sup>          |
| Total cholesterol (mg/dl), $n$                                                                                                       | 184.51 $\pm$ 45.30, 854                 | 167.47 $\pm$ 40.71, 491              | 167.81 $\pm$ 46.11, 101                       | < 0.0001 <sup>d</sup>          |

Table 1 continued

| Continuous variables described as mean $\pm$ standard deviation; categorical variables described as frequency (percent) <sup>b</sup> | Non-elderly (< 65 years) (N = 5892) | Elderly (65–79 years) (N = 4143) | Very elderly ( $\geq$ 80 years) (N = 911) | Global <i>p</i> -value <sup>c</sup> |
|--------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|----------------------------------|-------------------------------------------|-------------------------------------|
| HDL cholesterol (mg/dl), <i>n</i>                                                                                                    | 52.48 $\pm$ 19.37, 736              | 51.20 $\pm$ 17.65, 397           | 52.98 $\pm$ 18.08, 82                     | 0.4841 <sup>d</sup>                 |
| LDL cholesterol (mg/dl), <i>n</i>                                                                                                    | 111.76 $\pm$ 39.14, 674             | 97.96 $\pm$ 34.87, 347           | 101.09 $\pm$ 36.24, 78                    | < 0.0001 <sup>d</sup>               |
| Triglyceride (mg/dl), <i>n</i>                                                                                                       | 178.74 $\pm$ 107.56, 750            | 142.08 $\pm$ 73.36, 416          | 140.58 $\pm$ 96.02, 85                    | < 0.0001 <sup>d</sup>               |
| Glucose (mg/dl), <i>n</i>                                                                                                            | 125.99 $\pm$ 45.01, 894             | 128.40 $\pm$ 43.41, 534          | 127.31 $\pm$ 36.57, 108                   | 0.0519 <sup>d</sup>                 |
| Medication history                                                                                                                   |                                     |                                  |                                           |                                     |
| Number of prior antihypertensive drugs <sup>f</sup>                                                                                  |                                     |                                  |                                           | < 0.0001 <sup>c</sup>               |
| 0                                                                                                                                    | 1905 (32.33)                        | 1118 (26.99)                     | 227 (24.92)                               |                                     |
| 1                                                                                                                                    | 1122 (19.04)                        | 966 (23.32)                      | 217 (23.82)                               |                                     |
| 2                                                                                                                                    | 1968 (33.40)                        | 1346 (32.49)                     | 275 (30.19)                               |                                     |
| 3                                                                                                                                    | 666 (11.30)                         | 527 (12.72)                      | 134 (14.71)                               |                                     |
| $\geq 4$                                                                                                                             | 231 (3.92)                          | 186 (4.49)                       | 58 (6.37)                                 |                                     |
| Antihypertensive drugs used prior <sup>g</sup>                                                                                       |                                     |                                  |                                           |                                     |
| ACE inhibitor or ARB                                                                                                                 | 3247 (55.11)                        | 2381 (57.47)                     | 542 (59.50)                               | 0.0088 <sup>c</sup>                 |
| Calcium channel blocker                                                                                                              | 2724 (46.23)                        | 1933 (46.66)                     | 434 (47.64)                               | 0.7095 <sup>c</sup>                 |
| Thiazide or thiazide-like diuretics                                                                                                  | 797 (13.53)                         | 600 (14.48)                      | 159 (17.45)                               | 0.0056 <sup>c</sup>                 |
| Loop diuretic                                                                                                                        | 60 (1.02)                           | 80 (1.93)                        | 39 (4.28)                                 | < 0.0001 <sup>c</sup>               |
| MCRA                                                                                                                                 | 46 (0.78)                           | 29 (0.70)                        | 8 (0.88)                                  | 0.8185 <sup>d</sup>                 |
| Beta blocker                                                                                                                         | 931 (15.80)                         | 799 (19.29)                      | 186 (20.42)                               | < 0.0001 <sup>c</sup>               |
| Alpha blocker                                                                                                                        | 34 (0.58)                           | 24 (0.58)                        | 2 (0.22)                                  | 0.3737 <sup>c</sup>                 |

*HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *ACE* angiotensin-converting enzyme, *ARB* angiotensin receptor blocker, *MCRA* mineralocorticoid receptor antagonist

<sup>a</sup>Excluding two patients with missing age data

<sup>b</sup>Percentage denominators are the number of subjects at each group with data and exclude those with missing data

<sup>c</sup>*P*-value for three age groups by: <sup>d</sup>Kruskal-Wallis test; <sup>e</sup>chi-square test

<sup>f</sup>The previous number of antihypertensive drugs was defined by the number of pills used before enrollment in previous observational studies, with single agents and fixed-dose drug combinations both counted as one drug (one pill)

<sup>g</sup>One study subject may have two or more items

Elderly and very elderly patients did not have higher relative risk (RR) compared with non-elderly patients when stratified by baseline SBP or DBP (Table 2).

Among patients aged  $\geq 65$  years, hypotension-related AEs occurred in 4.11% (95% CI

3.45, 4.86), 3.91% (95% CI 2.78, 5.33), and 3.33% (95% CI 2.05, 5.10) of those treated with O/A/H 5/20/12.5 mg, 5/40/12.5 mg, and 10/40/12.5 mg, respectively (Table 3). The relative risk of AEs did not differ significantly across dosage groups, including

**Table 2** Hypotension-related adverse events, by age group

| Age group    |                           | Incidence rate         |                       | Relative risk (95% CI)  |                       |
|--------------|---------------------------|------------------------|-----------------------|-------------------------|-----------------------|
|              |                           | Patients, <i>n</i> (%) | (95% CI) <sup>a</sup> | Unadjusted <sup>b</sup> | Adjusted <sup>c</sup> |
| Overall      |                           |                        |                       |                         |                       |
|              | Non-elderly (< 65 years)  | 284 (4.82)             | (4.29, 5.40)          | 1 (Reference)           | 1 (Reference)         |
|              | Elderly (65–79 years)     | 184 (4.44)             | (3.83, 5.11)          | 0.92 (0.77, 1.10)       | 0.79 (0.62, 1.00)     |
|              | Very elderly (≥ 80 years) | 42 (4.61)              | (3.34, 6.18)          | 0.96 (0.70, 1.31)       | 0.71 (0.46, 1.12)     |
| Baseline SBP |                           |                        |                       |                         |                       |
| < 140 mmHg   | Non-elderly (< 65 years)  | 21 (4.82)              | (3.01, 7.27)          | 1 (Reference)           | 1 (Reference)         |
|              | Elderly (65–79 years)     | 2 (2.38)               | (0.29, 8.34)          | 0.49 (0.12, 2.07)       | NE                    |
|              | Very elderly (≥ 80 years) | 0 (0.00)               | (0.00, 30.85)         | 0.00 (0.00, 0.00)       | NE                    |
| 140–149 mmHg | Non-elderly (< 65 years)  | 86 (4.22)              | (3.39, 5.18)          | 1 (Reference)           | 1 (Reference)         |
|              | Elderly (65–79 years)     | 70 (4.56)              | (3.57, 5.73)          | 1.08 (0.80, 1.47)       | 0.79 (0.53, 1.17)     |
|              | Very elderly (≥ 80 years) | 16 (5.54)              | (3.20, 8.84)          | 1.31 (0.78, 2.21)       | 0.78 (0.36, 1.65)     |
| 150–159 mmHg | Non-elderly (< 65 years)  | 83 (5.01)              | (4.01, 6.17)          |                         | 1 (Reference)         |
|              | Elderly (65–79 years)     | 55 (4.49)              | (3.40, 5.81)          | 0.90 (0.64, 1.25)       | 0.85 (0.56, 1.31)     |
|              | Very elderly (≥ 80 years) | 9 (3.31)               | (1.52, 6.19)          | 0.66 (0.34, 1.30)       | NE                    |
| ≥ 160 mmHg   | Non-elderly (< 65 years)  | 94 (5.35)              | (4.34, 6.50)          | 1 (Reference)           | 1 (Reference)         |
|              | Elderly (65–79 years)     | 57 (4.38)              | (3.33, 5.64)          | 0.82 (0.59, 1.13)       | 0.80 (0.52, 1.22)     |
|              | Very elderly (≥ 80 years) | 17 (5.00)              | (2.94, 7.88)          | 0.94 (0.57, 1.55)       | 0.80 (0.39, 1.66)     |
| Baseline DBP |                           |                        |                       |                         |                       |
| < 90 mmHg    | Non-elderly (< 65 years)  | 87 (4.24)              | (3.41, 5.21)          | 1 (Reference)           | 1 (Reference)         |
|              | Elderly (65–79 years)     | 111 (4.26)             | (3.51, 5.10)          | 1.00 (0.76, 1.32)       | 0.78 (0.55, 1.11)     |
|              | Very elderly (≥ 80 years) | 36 (5.84)              | (4.13, 8.00)          | 1.38 (0.94, 2.01)       | 0.89 (0.51, 1.54)     |

Table 2 continued

| Age group  |                           | Incidence rate         |                       | Relative risk (95% CI)  |                       |
|------------|---------------------------|------------------------|-----------------------|-------------------------|-----------------------|
|            |                           | Patients, <i>n</i> (%) | (95% CI) <sup>a</sup> | Unadjusted <sup>b</sup> | Adjusted <sup>c</sup> |
| 90–94 mmHg | Non-elderly (< 65 years)  | 70 (5.11)              | (4.00, 6.41)          | 1 (Reference)           | 1 (Reference)         |
|            | Elderly (65–79 years)     | 33 (4.45)              | (3.08, 6.19)          | 0.87 (0.58, 1.30)       | 0.92 (0.56, 1.51)     |
|            | Very elderly (≥ 80 years) | 2 (1.36)               | (0.17, 4.83)          | 0.27 (0.07, 1.07)       | 0.20 (0.03, 1.46)     |
| 95–99 mmHg | Non-elderly (< 65 years)  | 38 (4.48)              | (3.19, 6.10)          | 1 (Reference)           | 1 (Reference)         |
|            | Elderly (65–79 years)     | 17 (5.18)              | (3.05, 8.17)          | 1.16 (0.66, 2.02)       | 0.69 (0.31, 1.53)     |
|            | Very elderly (≥ 80 years) | 1 (1.69)               | (0.04, 9.09)          | 0.38 (0.05, 2.71)       | 0.40 (0.05, 3.03)     |
| ≥ 100 mmHg | Non-elderly (< 65 years)  | 89 (5.48)              | (4.42, 6.70)          | 1 (Reference)           | 1 (Reference)         |
|            | Elderly (65–79 years)     | 23 (4.95)              | (3.16, 7.33)          | 0.90 (0.58, 1.41)       | 0.88 (0.50, 1.55)     |
|            | Very elderly (≥ 80 years) | 3 (3.37)               | (0.70, 9.54)          | 0.62 (0.20, 1.91)       | 0.58 (0.15, 2.35)     |

CI confidence interval, DBP diastolic blood pressure, SBP systolic blood pressure, NE not evaluated, O/A/H olmesartan medoxomil/amlodipine besylate/hydrochlorothiazide

<sup>a</sup>95% confidence interval calculated using Clopper-Pearson exact method

<sup>b</sup>Relative risk by logistic regression analysis where the covariate variable is O/A/H dose group

<sup>c</sup>Relative risk by logistic regression analysis (covariate variables: O/A/H dose group, age, sex, body mass index, smoking status, cardiovascular disease, diabetes mellitus, chronic kidney disease)

after stratification by baseline SBP and DBP (Table 3).

In the non-elderly subgroup (< 65 years), hypotension-related AEs occurred in 4.44% (95% CI 3.79, 5.17) of patients receiving O/A/H 5/20/12.5 mg, 4.26% (95% CI 3.19, 5.56) receiving 5/40/12.5 mg, and 2.76% (95% CI 1.76, 4.11) receiving 10/40/12.5 mg (Table S5). Unadjusted RR of hypotension-related AEs was lower in the 10/40/12.5 mg group than in the 5/20/12.5 mg group (RR 0.62, 95% CI 0.40, 0.96), but the adjusted risk was not statistically significant (RR 0.77, 95% CI 0.47, 1.24). Stratified analyses by baseline SBP or DBP also showed no significant dose-dependent trend in AE incidence (Table S5).

The adjusted risk of hypotension-related AEs did not differ significantly between patients

aged < 65 and ≥ 65 years, regardless of the number of prior antihypertensive medications (Table S6). The incidence of hypotension-related AEs was comparable between patients who achieved target BP and those who did not, in both patients aged ≥ 65 years (4.99% vs. 4.31%) and the very elderly group (4.64% vs. 4.60%) (Table S7). However, patients aged ≥ 65 years who achieved target BP had lower adjusted risk of AEs relative to those < 65 years old (RR 0.53, 95% CI 0.32, 0.85).

We also analyzed the frequency of O/A/H discontinuations due to specific AEs, including individual components of the composite endpoint (Table S8). These rates were < 3% across age groups; there were no discontinuations due to falls and only three for fractures (one non-elderly, two elderly).

**Table 3** Hypotension-related adverse events in geriatric patients ( $\geq 65$  years), by O/A/H dose

| Geriatric patients<br>( $\geq 65$ years) | O/A/H dose (mg) | Incidence rate         |                       | Relative risk (95% CI)  |                       |
|------------------------------------------|-----------------|------------------------|-----------------------|-------------------------|-----------------------|
|                                          |                 | Patients, <i>n</i> (%) | (95% CI) <sup>a</sup> | Unadjusted <sup>b</sup> | Adjusted <sup>c</sup> |
| Overall                                  | 5/20/12.5       | 132 (4.11)             | (3.45, 4.86)          | 1 (Reference)           | 1 (Reference)         |
|                                          | 5/40/12.5       | 38 (3.91)              | (2.78, 5.33)          | 0.95 (0.67, 1.36)       | 0.81 (0.50, 1.31)     |
|                                          | 10/40/12.5      | 20 (3.33)              | (2.05, 5.10)          | 0.81 (0.51, 1.29)       | 0.90 (0.51, 1.56)     |
| Baseline SBP                             |                 |                        |                       |                         |                       |
| < 140 mmHg                               | 5/20/12.5       | 1 (1.64)               | (0.04, 8.80)          | 1 (Reference)           | 1 (Reference)         |
|                                          | 5/40/12.5       | 1 (4.35)               | (0.11, 21.95)         | 2.65 (0.17, 40.67)      | NE                    |
|                                          | 10/40/12.5      | 0 (0.00)               | (0.00, 40.96)         | NE                      | NE                    |
| 140–149 mmHg                             | 5/20/12.5       | 51 (4.27)              | (3.20, 5.58)          | 1 (Reference)           | 1 (Reference)         |
|                                          | 5/40/12.5       | 17 (4.94)              | (2.90, 7.79)          | 1.16 (0.68, 1.98)       | NE                    |
|                                          | 10/40/12.5      | 9 (4.62)               | (2.13, 8.58)          | 1.08 (0.54, 2.16)       | NE                    |
| 150–159 mmHg                             | 5/20/12.5       | 37 (3.83)              | (2.71, 5.24)          | 1 (Reference)           | 1 (Reference)         |
|                                          | 5/40/12.5       | 12 (4.18)              | (2.18, 7.19)          | 1.09 (0.58, 2.07)       | NE                    |
|                                          | 10/40/12.5      | 4 (2.41)               | (0.66, 6.05)          | 0.63 (0.23, 1.74)       | NE                    |
| $\geq 160$ mmHg                          | 5/20/12.5       | 43 (4.35)              | (3.17, 5.82)          | 1 (Reference)           | 1 (Reference)         |
|                                          | 5/40/12.5       | 8 (2.52)               | (1.10, 4.91)          | 0.58 (0.28, 1.22)       | NE                    |
|                                          | 10/40/12.5      | 7 (3.02)               | (1.22, 6.12)          | 0.69 (0.32, 1.52)       | NE                    |
| Baseline DBP                             |                 |                        |                       |                         |                       |
| < 90 mmHg                                | 5/20/12.5       | 82 (4.03)              | (3.22, 4.98)          | 1 (Reference)           | 1 (Reference)         |
|                                          | 5/40/12.5       | 28 (4.42)              | (2.95, 6.32)          | 1.10 (0.72, 1.67)       | 1.00 (0.57, 1.76)     |
|                                          | 10/40/12.5      | 13 (3.32)              | (1.78, 5.62)          | 0.82 (0.46, 1.47)       | 0.90 (0.45, 1.80)     |
| 90–94 mmHg                               | 5/20/12.5       | 20 (3.40)              | (2.09, 5.20)          | 1 (Reference)           | 1 (Reference)         |
|                                          | 5/40/12.5       | 6 (3.95)               | (1.46, 8.39)          | 1.16 (0.48, 2.84)       | 0.87 (0.25, 2.99)     |
|                                          | 10/40/12.5      | 4 (4.00)               | (1.10, 9.93)          | 1.18 (0.41, 3.37)       | 1.66 (0.56, 4.92)     |
| 95–99 mmHg                               | 5/20/12.5       | 12 (4.71)              | (2.45, 8.08)          | 1 (Reference)           | 1 (Reference)         |
|                                          | 5/40/12.5       | 1 (1.47)               | (0.04, 7.92)          | 0.31 (0.04, 2.36)       | NE                    |
|                                          | 10/40/12.5      | 1 (2.44)               | (0.06, 12.86)         | 0.52 (0.07, 3.88)       | NE                    |

Table 3 continued

| Geriatric patients<br>(≥ 65 years) | O/A/H dose (mg) | Incidence rate         |                       | Relative risk (95% CI)  |                       |
|------------------------------------|-----------------|------------------------|-----------------------|-------------------------|-----------------------|
|                                    |                 | Patients, <i>n</i> (%) | (95% CI) <sup>a</sup> | Unadjusted <sup>b</sup> | Adjusted <sup>c</sup> |
| ≥ 100 mmHg                         | 5/20/12.5       | 18 (5.42)              | (3.24, 8.43)          | 1 (Reference)           | 1 (Reference)         |
|                                    | 5/40/12.5       | 3 (2.56)               | (0.53, 7.31)          | 0.47 (0.14, 1.58)       | NE                    |
|                                    | 10/40/12.5      | 2 (2.94)               | (0.36, 10.22)         | 0.54 (0.13, 2.28)       | NE                    |

CI confidence interval, NE not evaluated, O/A/H olmesartan medoxomil/amlodipine besylate/hydrochlorothiazide, SBP systolic blood pressure, DBP diastolic blood pressure

<sup>a</sup>95% Confidence interval was calculated using the Clopper-Pearson exact method

<sup>b</sup>Relative risk by logistic regression analysis where the covariate variable is O/A/H dose group

<sup>c</sup>Relative risk by logistic regression analysis (covariate variables: O/A/H dose group, age, sex, body mass index, smoking status, cardiovascular disease, diabetes mellitus, chronic kidney disease)

Sex and comorbidities were not significant predictors in a multivariable logistic regression analysis of elderly patients to identify risk factors for hypotension-related AEs (Table S9). However, higher BMI was independently associated with a lower risk of hypotension-related AEs (odds ratio 0.94 per 1 kg/m<sup>2</sup> increase, 95% CI 0.89–0.99,  $p=0.0198$ ).

### Effectiveness Outcomes

Reductions in SBP, DBP, and pulse pressure were observed in all age groups, beginning by Week 8 and sustained through Week 24 (Fig. 2). At Week 24, the mean BP was < 140/90 mmHg in all dosage groups, and pulse pressure was also reduced compared to baseline.

Across O/A/H dosage groups, patients ≥ 65 years old had mean SBP reductions from baseline of – 20.34 mmHg for 5/20/12.5 mg, – 18.84 mmHg for 5/40/12.5 mg, and – 19.25 mmHg for 10/40/12.5 mg (Table 4). ANCOVA analysis showed no statistically significant difference in SBP, DBP, or pulse pressure reduction between dosage groups in patients either ≥ 65 or < 65 years old (Tables 4, S10). In multivariable linear regression analyses to assess determinants of SBP reduction at Week 24, O/A/H dosage was not significantly associated with SBP change (Tables S11-1 and S11-2). Greater SBP reductions were associated with a higher number of previously used antihypertensive agents

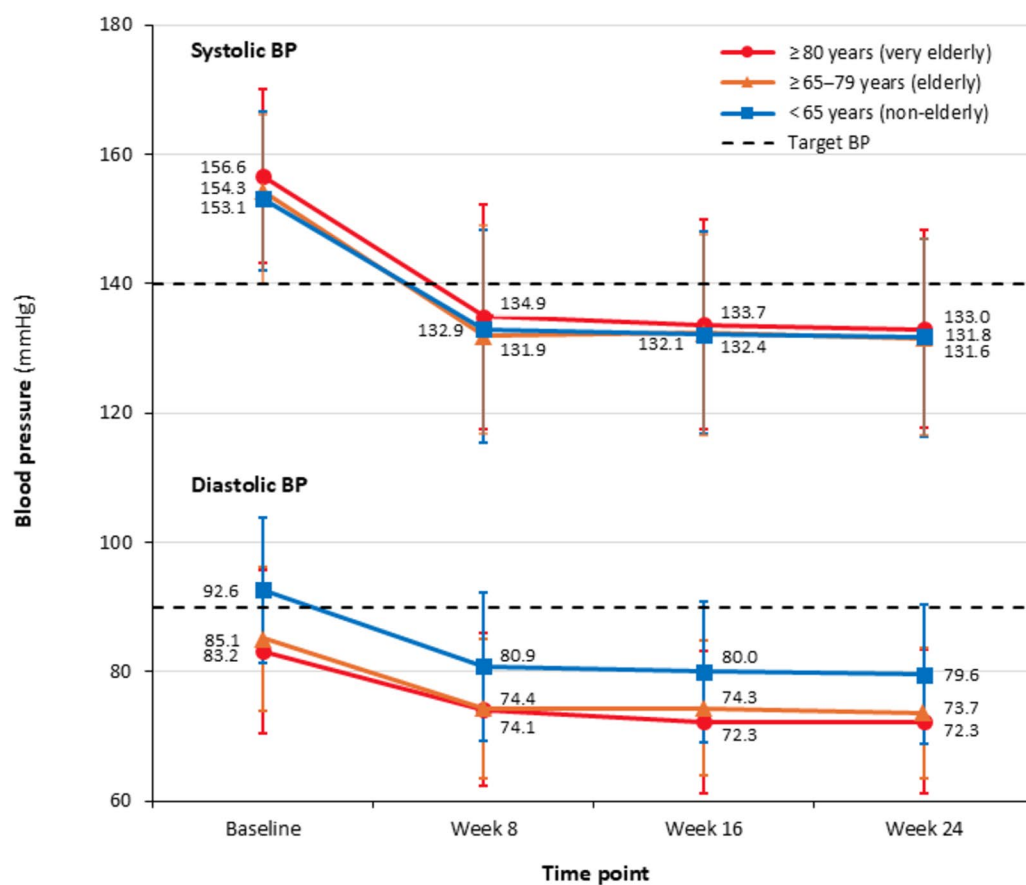
(e.g., ≥ 3 agents:  $\beta=9.48$ ,  $p<0.0001$ ) and higher BMI ( $\beta=0.26$ ,  $p=0.0456$ ) (Table S11-1). Regarding types of prior antihypertensive drugs, SBP reductions were associated with use of calcium channel blockers ( $\beta=5.69$ ,  $p<0.0001$ ) and beta-blockers ( $\beta=3.91$ ,  $p=0.0070$ ) (Table S11-2).

Effectiveness was also consistent regardless of prior treatment history; substantial SBP reductions were observed in treatment-naïve patients as well as those switching from multiple agents (Tables S12, S13, S14). In addition, the mean DBP remained > 70 mmHg after 24 weeks regardless of age group, O/A/H dose, or prior medication use (Tables 4, S10, S12, S13, S14). Additionally, regarding the O/A/H dose response, the sensitivity analysis excluding patients who used antihypertensive medications concomitant with O/A/H also found no significant difference in SBP reductions across dosage groups ( $p>0.05$ ) (Tables S15, S16).

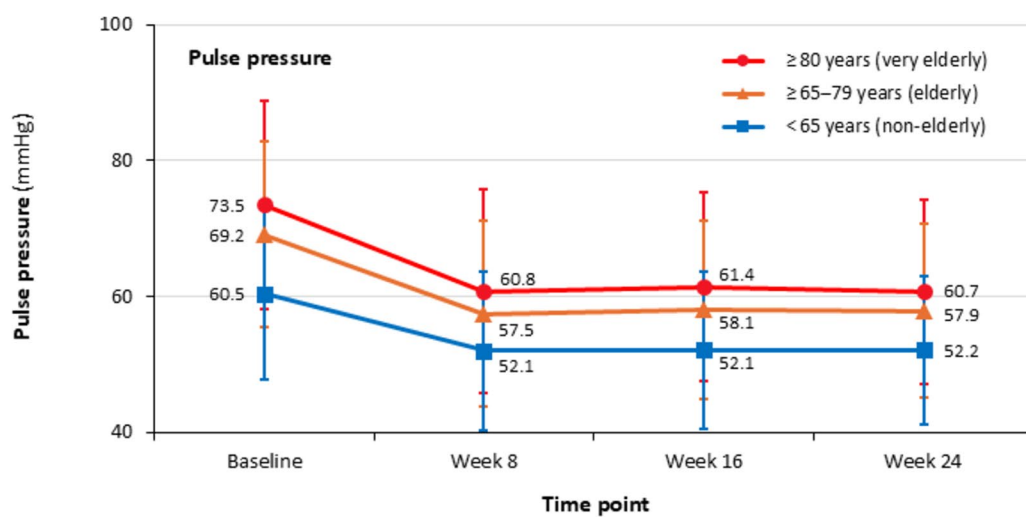
## DISCUSSION

This pooled analysis of three large-scale, real-world prospective studies (RESOLVE, RESOLVE-PRO, and RESOLVE-INT) [18–20] provides a comprehensive evaluation of the safety and effectiveness of O/A/H SPC therapy in older patients with hypertension. Across age groups and doses, O/A/H was consistently well

A.



B.



| Age (years)         | Baseline | Week 8 | Week 16 | Week 24 |
|---------------------|----------|--------|---------|---------|
| ≥ 80 (very elderly) | 754      | 306    | 418     | 294     |
| ≥ 65–79 (elderly)   | 3,578    | 1,460  | 2,003   | 1,426   |
| < 65 (non-elderly)  | 4,959    | 2,182  | 2,682   | 1,808   |

◀**Fig. 2** Blood pressure change in patients treated for 24 weeks with O/A/H, stratified by age. **A** Systolic and diastolic BP; **B** pulse pressure. BP blood pressure, O/A/H olmesartan medoxomil/amlodipine besylate/hydrochlorothiazide. Dashed lines indicate guideline targets for systolic BP (< 140 mmHg) and diastolic BP (< 90 mmHg). Table below shows the number of patients remaining for analysis at each timepoint

tolerated, with modest rates of hypotension-related AEs and no indication of increased risk associated with either increasing age or the O/A/H dose. The antihypertensive effect of O/A/H was robust—clinically meaningful reductions in SBP, DBP, and pulse pressure were achieved early and sustained throughout the 24-week observation period. By Week 24, all treatment groups achieved mean BP values below the thresholds recommended by current guidelines, supporting the real-world efficacy of O/A/H SPC.

The safety and efficacy findings of this real-world study align with and extend those of landmark trials of intensive BP control. In the SPRINT senior subgroup ( $\geq 75$  years), intensive BP control (SBP target < 120 mmHg) significantly reduced the risk of major CV outcomes and all-cause mortality, without a statistically significant increase in hypotension, syncope, or falls, although these events were more numerous [24]. Similarly, the STEP trial in Chinese adults aged 60–80 years demonstrated a 26% reduction in major CV events with an intensive SBP target (110 to < 130 mmHg) and a modest but statistically significant increase in hypotension (3.4% vs. 2.6%) [10]. Dizziness, syncope, and fractures did not differ significantly between groups.

In contrast to these trials, our study evaluated the use of O/A/H SPC in a real-world cohort that included patients typically excluded from RCTs, such as those with diabetes, prior stroke, or cognitive impairment. This patient population is likely to have lower physiological reserve and a higher baseline risk of orthostatic hypotension, falls, and syncope, particularly among those aged  $\geq 75$  years [26, 27]. Nevertheless, the overall safety profile in our study aligns with those observed in SPRINT [24] and STEP [10] and is supported by recent evidence that intensive BP management does not increase orthostatic

hypotension risk in older adults [14]. Although our definition of hypotension-related AEs—composite hypotension, dizziness, syncope, and falls or fractures—limits direct comparison to SPRINT and STEP, which reported these AEs separately, the incidence of approximately 4–5% in our study, seems comparable to 3.4% for hypotension alone in the STEP intensive SBP control arm. In addition, a small observational study that compared O/A/H SPC with a two-pill equivalent reported no episodes of hypotension and only mild adverse drug reactions, such as dizziness or fatigue [28]. Another study, in 401 Chinese adults aged  $\geq 60$  years, found that frailty and hypertension were independently and jointly associated with increased fall risk and that appropriate hypertension management may mitigate this risk [29]. Regarding frailty, although direct scores were not available in our study data, we analyzed surrogate markers including BMI. Interestingly, we observed an inverse relationship where higher BMI was associated with a lower risk of adverse events (Table S9). This is consistent with the "obesity paradox" that is often apparent in elderly people, where higher BMI may reflect better nutritional status and physiological reserve, whereas lower BMI may be a surrogate marker for frailty or sarcopenia.

Contrary to prior efficacy findings, we did not observe the anticipated dose-response gradient in SBP reduction. While this may appear inconsistent with pharmacological expectations, our sensitivity analysis excluding concomitant medications confirmed that this was not because of other drug effects. Rather, the results of multivariable regression suggested "confounding by indication." Further analysis revealed that the treatment response was more strongly influenced by patient-level characteristics than by SPC dose alone. In multivariable models, higher BMI and prior use of calcium channel blockers, beta-blockers, and multiple antihypertensive agents were positive predictors of attenuated SBP reduction (Tables S11-1, S11-2). This suggests that the incremental dose response to O/A/H may have been obscured because higher doses were preferentially prescribed to patients with more resistant or difficult-to-treat hypertension.

**Table 4** Blood pressure change from baseline to week 24 in geriatric patients ( $\geq 65$  years), by O/A/H dose

| Geriatric patients ( $\geq 65$ years) |               | Baseline           | Week 24            | Least squares<br>mean $\pm$ SE | 95% CI for LS<br>mean | P-value <sup>a</sup> |
|---------------------------------------|---------------|--------------------|--------------------|--------------------------------|-----------------------|----------------------|
| Systolic blood pressure               |               |                    |                    |                                |                       |                      |
| O/A/H dose                            | SBP (mmHg)    |                    |                    |                                |                       |                      |
| 5/20/12.5 mg                          |               |                    |                    |                                |                       | Reference            |
|                                       | Number        | 2234               | 891                |                                |                       |                      |
|                                       | Mean $\pm$ SD | 152.67 $\pm$ 12.68 | 130.21 $\pm$ 14.43 |                                |                       |                      |
|                                       | Change        |                    | -22.51 $\pm$ 17.14 | -20.34 $\pm$ 0.97              | -22.23, -18.44        |                      |
| 5/40/12.5 mg                          |               |                    |                    |                                |                       | 0.4419               |
|                                       | Number        | 754                | 269                |                                |                       |                      |
|                                       | Mean $\pm$ SD | 152.66 $\pm$ 13.12 | 132.87 $\pm$ 15.17 |                                |                       |                      |
|                                       | Change        |                    | -18.80 $\pm$ 17.74 | -18.84 $\pm$ 1.28              | -21.35, -16.33        |                      |
| 10/40/12.5 mg                         |               |                    |                    |                                |                       | 0.7392               |
|                                       | Number        | 521                | 172                |                                |                       |                      |
|                                       | Mean $\pm$ SD | 154.66 $\pm$ 13.94 | 135.44 $\pm$ 16.29 |                                |                       |                      |
|                                       | Change        |                    | -19.13 $\pm$ 19.76 | -19.25 $\pm$ 1.49              | -22.17, -16.34        |                      |
| Diastolic blood pressure              |               |                    |                    |                                |                       |                      |
| O/A/H dose                            | DBP (mmHg)    |                    |                    |                                |                       |                      |
| 5/20/12.5mg                           |               |                    |                    |                                |                       | Reference            |
|                                       | Number        | 2017               | 831                |                                |                       |                      |
|                                       | Mean $\pm$ SD | 85.37 $\pm$ 11.15  | 73.83 $\pm$ 10.13  |                                |                       |                      |
|                                       | Change        |                    | -11.33 $\pm$ 12.73 | -10.95 $\pm$ 0.70              | -12.32, -9.58         |                      |
| 5/40/12.5 mg                          |               |                    |                    |                                |                       | 0.9828               |
|                                       | Number        | 610                | 251                |                                |                       |                      |
|                                       | Mean $\pm$ SD | 85.82 $\pm$ 11.75  | 73.78 $\pm$ 10.26  |                                |                       |                      |
|                                       | Change        |                    | -11.18 $\pm$ 12.07 | -11.12 $\pm$ 0.92              | -12.92, -9.31         |                      |
| 10/40/12.5 mg                         |               |                    |                    |                                |                       | 0.2754               |
|                                       | Number        | 375                | 144                |                                |                       |                      |
|                                       | Mean $\pm$ SD | 84.00 $\pm$ 11.20  | 72.57 $\pm$ 11.16  |                                |                       |                      |
|                                       | Change        |                    | -13.05 $\pm$ 13.37 | -12.72 $\pm$ 1.18              | -15.03, -10.41        |                      |
| Pulse pressure                        |               |                    |                    |                                |                       |                      |
| O/A/H dose                            | PP (mmHg)     |                    |                    |                                |                       |                      |

**Table 4** continued

| Geriatric patients ( $\geq 65$ years) | Baseline          | Week 24             | Least squares<br>mean $\pm$ SE | 95% CI for LS<br>mean | <i>P</i> -value <sup>a</sup> |
|---------------------------------------|-------------------|---------------------|--------------------------------|-----------------------|------------------------------|
| 5/20/12.5 mg                          |                   |                     |                                |                       |                              |
| Number                                | 2017              | 831                 |                                |                       |                              |
| Mean $\pm$ SD                         | 68.27 $\pm$ 13.08 | 57.11 $\pm$ 12.25   |                                |                       |                              |
| Change                                |                   | – 11.33 $\pm$ 14.15 | – 10.67 $\pm$ 0.79             | – 12.22, – 9.12       |                              |
| 5/40/12.5 mg                          |                   |                     |                                |                       | 0.7942                       |
| Number                                | 610               | 251                 |                                |                       |                              |
| Mean $\pm$ SD                         | 69.05 $\pm$ 15.18 | 58.86 $\pm$ 12.71   |                                |                       |                              |
| Change                                |                   | – 11.73 $\pm$ 14.72 | – 11.35 $\pm$ 1.04             | – 13.39, – 9.30       |                              |
| 10/40/12.5 mg                         |                   |                     |                                |                       | 0.8848                       |
| Number                                | 375               | 144                 |                                |                       |                              |
| Mean $\pm$ SD                         | 72.14 $\pm$ 13.88 | 60.65 (13.76)       |                                |                       |                              |
| Change                                |                   | – 10.84 $\pm$ 15.49 | – 10.05 $\pm$ 1.33             | – 12.67, – 7.44       |                              |

*CI* confidence interval, *SD* standard deviation, *SE* standard error, *LS* least squares, *O/A/H* olmesartan medoxomil/amlodipine besylate/hydrochlorothiazide, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *PP* pulse pressure

<sup>a</sup>*P*-value between O/A/H dosage groups based on analysis of covariance (ANCOVA) adjusted for baseline characteristics and multiple comparisons by Tukey-Kramer test

Notably, our study included some treatment-naïve patients who initiated triple-combination therapy. Although this diverges from standard guidelines, our analysis (Table S4) showed that these patients had significantly higher baseline SBP (156.32 mmHg) than those using multiple antihypertensive agents. This suggests that the clinical decision to initiate intensive therapy was driven by the imperative to rapidly control severe hypertension. Importantly, this approach was effective (Tables 4, S10) and did not result in a significant increase in hypotension-related AEs (Tables S6), supporting the real-world viability of treating high-risk patients with O/A/H SPC.

The population of South Korea is aging rapidly, and the number of individuals living with hypertension and CVD is expected to increase substantially in the coming decades [30]. Effective BP control is crucial to mitigating the individual and societal burdens of these conditions [21, 22]. O/A/H SPC is a well-tolerated, clinically effective antihypertensive option that can be used across the age range, including very elderly

patients and those with multiple comorbidities. International guidelines have begun to address the unique needs of the oldest individuals. The 2023 ESH guidelines explicitly include recommendations for patients aged  $\geq 80$  years, while the 2024 ESC guidelines further extend clinical guidance to those aged  $\geq 85$  years. These evolving recommendations underscore the need for robust, age-specific data in populations beyond the traditional scope of RCTs. In this context, our study has contributed important evidence by evaluating the real-world safety and effectiveness of SPC therapy, including in patients aged  $\geq 80$  years, who are often underrepresented in clinical trials. Given rapid population aging, especially in East Asia, and recent refinements of international guidelines, including very elderly patients in treatment evaluations is increasingly critical for informing clinical practice and public health strategy.

Our study has several important strengths, including its large sample size ( $> 10,000$  patients), inclusion of real-world clinical settings

across South Korea, and mid-term follow-up over 6–12 months. However, we acknowledge several limitations. First, this pooled analysis integrated data from observational studies with different designs (prospective and retrospective), which inherently limits causal inference. Second, identifying AEs through routine clinical records in observational studies may result in underreporting compared with active surveillance, as used in RCTs, warranting cautious interpretation of safety results. Third, blood pressure was measured using standard sphygmomanometers in routine clinical practice rather than following a standardized protocol (e.g., SPRINT), which could introduce biases because of factors such as the white-coat effect; although specific measurement protocols (e.g., number of readings) may have varied by site according to routine practice, this approach reflects real-world "office BP" monitoring. Fourth, detailed records of the exact dosages of prior antihypertensive medications were unavailable, precluding a quantitative analysis of dose increments. To address this limitation, we analyzed outcomes stratified by the number of prior agents, which showed consistent safety and effectiveness regardless of treatment history. Additionally, the observational nature of this study introduces potential confounding by indication, which may explain the lack of a clear dose-response relationship and the use of triple-combination therapy in treatment-naïve patients. Nevertheless, our subgroup analysis indicated that treatment-naïve patients had significantly higher baseline BP, suggesting that intensive initial therapy was a clinical decision based on disease severity rather than inappropriate prescribing. Finally, although the dataset included > 10,000 patients sampled from approximately 50 sites across Korea, the findings reflect safety and efficacy in routine clinical practice at the participating sites and should not be interpreted as establishing national prescribing practice for O/A/H.

Overall, our findings provide valuable insights into the safety and effectiveness of O/A/H SPC in older patients; however, they should be interpreted with caution and considered in the context of supporting evidence from RCTs. Further prospective studies are warranted to

confirm these observations and guide optimal use of O/A/H SPC therapy in high-risk elderly populations.

## CONCLUSION

This analysis of pooled real-world data showed that O/A/H SPC antihypertensive therapy was effective and well tolerated in elderly and very elderly South Korean patients with hypertension. BP control to < 140/90 mmHg was consistently achieved across all age groups, in line with current guideline targets. The incidence of hypotension-related AEs was low and did not increase with either age or SPC dose. These results suggest that concerns about hypotension should not preclude appropriate treatment in older adults. O/A/H SPC therapy offers a safe and practical option for controlling BP in the aging hypertensive population.

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ensure that any questions concerning its accuracy or integrity are resolved.

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**Data Availability.** The data that support the findings of this study are available from the corresponding author upon reasonable request.

### Declarations

**Conflict of Interest.** Hyun-Jin Kim and Hyue Mee Kim declare that they have no competing interests. Dae-Hee Kim has received honoraria from Viatrix, Organon, Boryoung, Hanmi, Daewoong, Celltrion, Daiichi Sankyo, and Chong Kun Dang, and a research grant from Daewoong.

**Ethical Approval.** The study protocol was approved by the Institutional Review Board of Asan Medical Center, Seoul, Republic of Korea (IRB no. 2024–0503) and was conducted in accordance with the principles of the Declaration of Helsinki 1964 and its later amendments, as well as the rules of the IRB. All patients voluntarily provided written informed consent before enrolling in the study. Study data were de-identified to protect the privacy of the participating patients and to comply with locally applicable regulations.

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