ORIGINAL RESEARCH

# Real-World Effectiveness and Safety of a Single-Pill Combination of Olmesartan/Amlodipine/ Hydrochlorothiazide in Korean Patients with Hypertension and Cardiovascular Risk Factors

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## ABSTRACT

*Introduction*: Patients with hypertension and additional cardiovascular risk factors pose a challenge by requiring more intensive blood pressure (BP) control. Single-pill combination (SPC) therapy can benefit these patients by improving medication adherence.

*Methods*: This prospective, multicenter observational study assessed the real-world safety and effectiveness of an SPC containing olmesartan, amlodipine, and hydrochlorothiazide (O/A/H) in South Korean patients with hypertension and cardiovascular risk factors. BP control rates, defined as the percentage of patients achieving systolic BP (SBP) < 130 mmHg and diastolic BP (DBP) < 80 mmHg for intensive BP control, and < 140 mmHg and < 90 mmHg, respectively, for standard BP control, were investigated across various cardiovascular risk groups, along with changes in SBP and DBP from baseline to week 24.

*Results*: The most prevalent cardiovascular risk factor was age ($\geq$ 45 years in men, $\geq$ 55 years in women, 86.1%), followed by cardiovascular diseases (64.4%), dyslipidemia (53.7%), body mass index $\geq$ 25 kg/m$^2$ (53.5%), and diabetes mellitus (DM) (46.3%). Switching to O/A/H showed significant BP reduction, with a mean

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change of − 17.8 mmHg/− 9.3 mmHg in SBP/DBP within 4 weeks. The intensive BP control rate was 41.4% (95% confidence interval [CI] 39.5, 43.4), and the standard BP control rate was 73.3% (95% CI 71.5, 75.1), with better control rates in the risk age group (43.1% and 74.1%, respectively) and cardiovascular disease group (42.0% and 73.8%, respectively). The DM group had relatively lower control rates (37.5% for intensive control and 69.4% for standard control). Common adverse drug reactions included dizziness (2.91%), hypotension (1.51%), and headaches (0.70%).

*Conclusion*: The SPC therapy of O/A/H caused a rapid and sustained reduction in SBP/DBP in patients' hypertension and additional cardiovascular risk factors. The therapy was safe and well tolerated.

*Study Registration Number*: KCT0003401 (https://cris.nih.go.kr/cris/search/detailSearch.do/20795).

Keywords: Olmesartan-based combination therapy; Single-pill combination; Patients with hypertension and additional cardiovascular risk factors; Real-world effectiveness of blood pressure control

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## Key Summary Points

### Why carry out this study?

Blood pressure (BP) control remains a challenge in some patients with hypertension, particularly in those with cardiovascular risk factors, who require more intensive BP control.

Single-pill combination (SPC) therapy has been proposed as a solution to improve poor medication adherence, which contributes to inadequate BP control, especially in patients taking multiple antihypertensive drugs.

This prospective, multicenter observational study assessed the real-world safety and effectiveness of an SPC containing olmesartan, amlodipine, and hydrochlorothiazide (O/A/H), in South Korean patients with hypertension and cardiovascular risk factors.

### What was learned from the study?

After switching to O/A/H, a mean reduction of − 17.8 mmHg/− 9.3 mmHg in systolic BP/diastolic BP was observed at 24 weeks ($P < 0.05$). The intensive BP control rate was 41.4% and the standard BP control rate was 73.3%. Intensive and standard BP control rates were relatively higher in the risk age group (43.1% and 74.1%, respectively) and cardiovascular disease group (42.0% and 73.8%, respectively) and relatively lower in the diabetes mellitus group (37.5% and 69.4%, respectively).

Patients with hypertension and additional cardiovascular risk factors benefit from O/A/H treatment. More intensive BP control is needed in patients with hypertension and diabetes mellitus, in line with the new treatment guidelines.

Among patients without prior calcium channel blockers (CCB) use (535 patients), the incidence of edema with O/A/H was 1.1%. The lower edema incidence in the present study may be attributed to excluding patients with a history of edema while using CCB before switching to O/A/H. Additionally, the concurrent administration of hydrochlorothiazide, which has diuretic properties, might have contributed to the lower edema incidence observed in this study.

## INTRODUCTION

Hypertension is a significant global health burden, affecting approximately 1.4 billion individuals worldwide and approximately 11 million cases in Korea alone [1, 2]. Although the prevalence of elevated blood pressure (BP) has been decreasing in recent decades, BP control among patients with hypertension remains poor, with fewer than 50% of them achieving target BP level [3, 4]. Poor medication adherence, especially in patients prescribed multiple antihypertensive drugs, is one of the reasons for the lack of adequate BP control [2, 3, 5].

Single-pill combination (SPC) therapy has been proposed as a solution to improve medication adherence by simplifying multidrug regimens. Numerous studies have demonstrated that SPC therapy improves medication adherence, leading to improved clinical outcomes in terms of BP control. Several meta-analyses and observational studies have shown the association between SPC therapy and a significant reduction in both systolic BP (SBP) and diastolic BP (DBP), with a higher percentage of patients achieving their target BP by improving adherence and persistence [6–9]. Based on these findings, recent guidelines recommend using SPC therapy as a first-line treatment in high-risk patients to achieve immediate BP response, improve tolerability, and increase medication adherence [5, 10, 11].

One such SPC therapy available worldwide is the triple combination of olmesartan, amlodipine, and hydrochlorothiazide (O/A/H), whose safety and efficacy have been demonstrated in numerous studies [12–15]. In the pivotal trial (TRINITY), O/A/H showed a greater least-square mean reduction in seated BP compared with the dual combination SPC in European patients with uncontrolled hypertension (SBP − 37.1 mmHg [O/A/H] vs. − 30.0 to − 27.5 mmHg [dual combination SPC], $P < 0.01$; DBP − 21.8 mmHg vs. − 18.0 to − 15.1 mmHg, $P < 0.01$) [12]. Recently, the RESOLVE and RESOLVE-PRO studies have provided real-world evidence of the safety and effectiveness of O/A/H in Asian patients with hypertension, demonstrating significant reductions in mean BP compared to baseline [16, 17].

Although the safety and efficacy (effectiveness) of O/A/H in the general population of patients with hypertension have been established, little is known about its effects on patients with hypertension and cardiovascular risk factors. Over 80% of patients with hypertension have at least one additional cardiovascular risk factor, with approximately half of them having more than two factors [18]. Notably, such patients require more intensive BP control than the general population of patients with hypertension to reduce the risk of cardiovascular disease (CVD) [19]. Confirming the safety and efficacy (effectiveness) of O/A/H in patients with hypertension and additional cardiovascular risk factors would allow these patients to benefit from SPC therapy. Therefore, we conducted a prospective, multicenter observational study to observe the safety and effectiveness of O/A/H in South Korean patients with hypertension and additional cardiovascular risk factors.

## METHODS

### Study Population

The study included adult individuals (≥ 19 years old) diagnosed with hypertension, for whom O/A/H was indicated under routine clinical practice, and who had at least one of the following cardiovascular risk factors defined by the 2013 Korean Society of Hypertension (KSH) guidelines (REF): age (≥ 45 years in men,

$\geq 55$ years in women), smoking, diabetes mellitus (DM), dyslipidemia, chronic kidney disease (CKD), or concurrent or history of CVD. Conversely, patients were excluded from the study if they had participated in other intervention studies, as this could potentially introduce confounding bias due to restrictions on medication use and the more intensive care setting compared to routine care. Furthermore, in order to mitigate potential bias arising from carryover effects stemming from previous use of O/A/H, we excluded patients who had previously taken O/A/H.

## Study Design and Procedures

This non-interventional, observational, multicenter, prospective cohort study was conducted between August 2018 and November 2020. A total of 63 investigators from 47 hospitals in Korea recruited patients and collected study-related information. Voluntary informed consent was obtained from O/A/H-naïve eligible patients. Patient demographics, medical histories, O/A/H prescription information, prior and other concurrent medications, and treatment-emergent adverse events (TEAEs) were collected from enrolled patients. Pre-specified cardiovascular risk factors were identified at baseline and subsequent follow-up visits. Baseline characteristics were assessed on the day of enrollment, and patients were followed up until week 24. Dose of O/A/H (20/5/12.5 mg, 40/5/12.5 mg, and 40/10/12.5 mg are approved doses in Korea) and the frequency of follow-up visits was not defined in the study protocol but was determined according to the routine clinical practice at each institution and the clinical judgement of the investigator. All data were de-identified to protect the privacy of participating patients and were captured in an electronic case report form. The study protocol and informed consent forms were approved by the institutional review board (IRB) of each participating institution. A list of IRB approval numbers is provided in Table S1. The study was conducted in accordance with the principles of the Declaration of Helsinki 1964 and its later amendments as well as the rules of each IRB.

## Effectiveness Endpoints

The primary endpoint was the intensive BP control rate, which was based on the 2017 American College of Cardiology/American Heart Association guidelines [11] and defined as the proportion of patients with SBP $< 130$ mmHg and DBP $< 80$ mmHg at week 24. The secondary endpoint was the standard BP control rate at week 24, which was defined as the proportion of patients with SBP $< 140$ mmHg and DBP $< 90$ mmHg based on the 2013 Korean Society of Hypertension (KSH) guidelines [20] and up-to-date local guidelines at the time of preparing the study protocol. Other secondary endpoints included changes in BP over time and changes in BP at week 24 from baseline.

## Safety Endpoints

TEAEs were collected and assessed to identify the safety and tolerability of O/A/Hs. TEAEs were assessed for seriousness, relationship with O/A/Hs, and expectedness. TEAEs with causalities assessed as certain, probable/likely, possible, conditional/unclassified, and unassessable/unclassifiable were considered as adverse drug reactions (ADRs). If a TEAE was not a known side effect of O/A/H, the event was classified as an unexpected TEAE, regardless of its relationship with O/A/H. Additionally, if a known adverse event listed in the product leaflet worsened in severity or recurred during the study period, the event was classified as an unexpected TEAE.

## Statistical Methods

For the sample size calculation, the intensive BP control rate was assumed to be 50%, which was based on a previous study in which 55–66% of patients achieved the intensive BP target (SBP/DBP $< 140/90$ mmHg) at any time of the study with two different-dose combinations of the O/A/H triple regimen [21]. A sample size of 2401 patients was calculated to observe 50% of patients achieving the intensive BP target with a precision of 4% at 95% confidence interval (CI).

Assuming a dropout rate of 20%, we targeted 3002 patients for registration.

Patient demographics and baseline characteristics were summarized using descriptive statistics. Continuous variables were presented as means, standard deviations (SD), medians, and ranges (minimum and maximum), whereas categorical variables were presented as frequencies and percentages.

Regarding the endpoints of intensive or standard BP control rate, the percentages of patients achieving the target BP at week 24 were calculated, along with their 95% CI, using the exact binomial method. Both intensive and standard BP control rates were presented for the following cardiovascular risk subgroups as well: risk age ($\geq$ 45 years in men, $\geq$ 55 years in women), smoking, BMI $\geq$ 25 kg/m$^2$, DM, dyslipidemia, CVD, and CKD.

Descriptive statistics were calculated for SBP and DBP values every 4 weeks from baseline until week 24. The statistical significance of the change in BP values from baseline to week 24 was tested using the paired $t$ test or Wilcoxon signed-rank test. Changes in BP at week 24 were further assessed in subgroups according to the use of previous antihypertensive drugs in terms of the number of drugs and combinations of drug classes. We also conducted additional analysis to ascertain the impact of enhanced medication adherence on BP reduction. Specifically, patients who employed an identical combination of antihypertensive medications as O/A/H were categorized on the basis of the quantity of pills (2-pill or 3-pill) consumed. Differences in BP changes at week 24 between the subgroups were compared using a two-sample $t$ test or Wilcoxon rank-sum test.

As a post hoc analysis, BP change at week 24 from baseline was summarized in the subgroups of elderly ($\geq$ 65 years), very elderly ($\geq$ 80 years), high-risk hypertension, CVD, high-risk CVD, high-risk DM, stroke, CKD with or without albuminuria, and CKD with DM. Two sets of BP control rates were also calculated on the basis of the intensive BP target used in the primary endpoint and the targets recommended in the 2022 KSH guidelines [22] for these subgroups. The definition and classification of the subgroups used for post hoc analysis were based on the 2022 KSH guidelines [22].

Adverse events were coded using MedDRA version 21.0. The rate of occurrence of TEAEs was calculated and presented with the number of events. TEAEs were further analyzed according to their seriousness, relationship with O/A/H, and expectedness. Effectiveness outcomes and baseline data were analyzed using an effectiveness analysis set, which comprised patients who received at least one dose of O/A/H and underwent BP measurement after week 20. Safety outcomes were analyzed using a safety analysis set, which comprised patients who received at least one dose of O/A/H and were assessed for safety at least once. All hypothesis testing was two-sided, and a $P$ value less than 0.5 was considered statistically significant. All statistical analyses were conducted using the Statistical Analysis Software (SAS) version 9.4 (SAS Institute Inc, Cary, North Carolina, USA).

# RESULTS

## Patient Characteristics

Among 3145 patients enrolled in the study, 2401 patients (76.3%) completed the 24-week follow-up period (Fig. 1). After 41 patients with missing measurements of SBP and/or DBP at 24 weeks were excluded, a total of 2360 patients were included in the effectiveness analysis set assessing the effectiveness endpoints. The demographic and clinical characteristics of the effectiveness analysis set are presented in Table 1. The mean age was 63.3 years, and 86.1% of the patients were included in the risk age group ($\geq$ 45 years in men, $\geq$ 55 years in women). Concurrent or history of CVDs was the second most prevalent cardiovascular risk factor (64.4%) in this study population, and when only the high-risk CVDs only were considered, more than half of the patients (51.5%) fell into this subgroup. Other cardiovascular risk factors (percentage of relevant patients) included, in the order of frequency, dyslipidemia (53.7%), obesity (BMI $\geq$ 25 kg/m$^2$) (53.5%), DM (46.3%), smoking (14.8%), and CKD (3.8%). As for prior
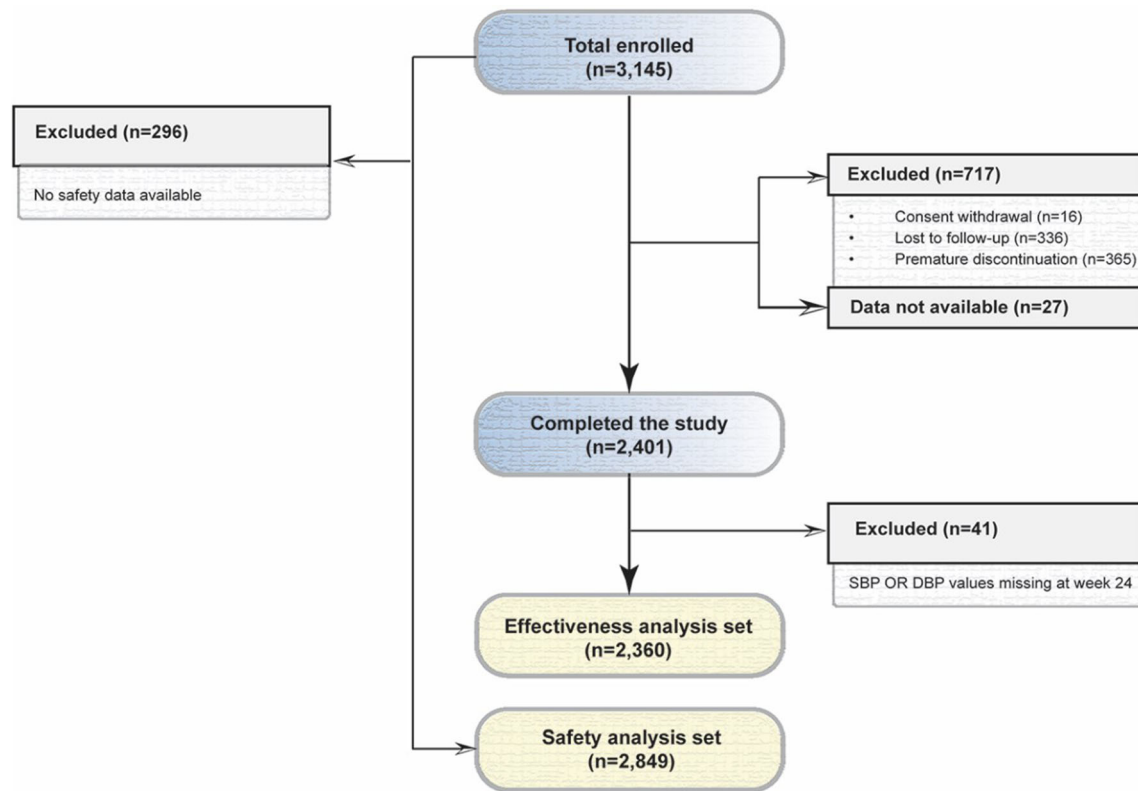
**Fig. 1** Patient selection process. *DBP* diastolic blood pressure, *SBP* systolic blood pressure

antihypertensive treatment, double-combination treatment was the most common strategy (45.8%).

**Treatment Exposure and Compliance**

In the effectiveness population, the mean treatment duration of O/A/H was 197 days (median 185 days). The most frequently prescribed dose-strength combination of O/A/H was 20/5/12.5 mg, given to 1558 patients (66.0%); meanwhile, 626 (26.5%) and 309 (13.1%) patients were prescribed 40/5/12.5 mg and 40/10/12.5 mg, respectively. Based on the total treatment duration and cumulative dose of O/A/H, the number of O/A/H tablets taken per day was approximately 1, as instructed in the approved label (Table 2).

**Effectiveness Outcomes**

At week 24, the intensive BP control rate was 41.4% (95% CI 39.5%, 43.4%), while the standard BP control rate was 73.3% (95% CI 71.5%, 75.1%). The mean baseline BP (SBP/DBP) was 146.9/83.9 mmHg, and both SBP and DBP values showed a decreasing trend from week 4, with the level of BP reduction maintained until week 24 (Fig. S1 in the supplementary material). Reductions in both SBP and DBP at week 24 were statistically significant ($P < 0.0001$), with a mean change of − 17.8 mmHg and − 9.3 mmHg for SBP and DBP, respectively (Table 3).

In the subgroups with different cardiovascular risks, the intensive BP control rate ranged from 36.8% to 43.1%. The risk age group had the highest intensive BP control rate at 43.1%, followed by the CVD group (42.0%) (Fig. 2). Regarding the standard BP control rates among the cardiovascular risk subgroups, the risk age

**Table 1** Demographics and clinical characteristics of patients at baseline

| | Effectiveness set ($n = 2360$) |
|---|---|
| Age, years | $63.3 \pm 13.2$ |
| < 45 | 226 (9.6) |
| 45–55 | 343 (14.5) |
| 55–65 | 630 (26.7) |
| 65–79 | 927 (39.3) |
| ≥ 80 | 234 (9.9) |
| Male, $n$ (%) | 1280 (54.2) |
| Height, cm | $162.8 \pm 9.4$ |
| Weight, kg | $70.7 \pm 14.0$ |
| Body mass index, kg/m$^2$ | $26.6 \pm 3.9$ |
| Systolic blood pressure, mmHg | $146.9 \pm 17.9$ |
| Diastolic blood pressure, mmHg | $83.9 \pm 13.3$ |
| Uncontrolled hypertension status[a] | 1718 (73.1) |
| Cardiovascular risk factors | |
| Age ≥ 45 years in men, ≥ 55 years in women | 2031 (86.1) |
| Smoking | 348 (14.8) |
| Body mass index ≥ 25 kg/m$^2$ | 1263 (53.5) |
| Diabetes mellitus | 1092 (46.3) |
| High-risk diabetes mellitus[b] | 1087 (46.1) |
| Dyslipidemia | 1267 (53.7) |
| Cardiovascular disease | 1520 (64.4) |
| High-risk cardiovascular disease [c] | 1216 (51.5) |
| Chronic kidney disease | 89 (3.8) |
| Chronic kidney disease without albuminuria | 57 (2.4) |
| Chronic kidney disease with albuminuria | 32 (1.4) |
| Chronic kidney disease with diabetes mellitus | 70 (3.0) |
| Antihypertensive medications prior to study | 2057 (87.2) |

**Table 1** continued

| | Effectiveness set ($n = 2360$) |
|---|---|
| Number of prior antihypertensive components | |
| 1 | 426 (18.1) |
| 2 | 1080 (45.8) |
| 3 | 459 (19.4) |
| ≥ 4 | 92 (3.9) |
| Antihypertensive SPC use prior to study | 1262 (53.5) |

Continuous variables are presented as means and standard deviations and categorical variables as frequencies and percentages

*SPC* single-pill combination therapy

[a]Uncontrolled hypertension status was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg at baseline

[b]High-risk diabetes mellitus was defined as diabetes mellitus with at least one cardiovascular risk factor

[c]High-risk cardiovascular disease was defined as patients aged ≥ 50 years with coronary artery disease, peripheral vascular disease, abdominal aortic aneurysm, heart failure, or left ventricular hypertrophy

group had the highest standard BP control rate at 74.1%, followed by the CVD group (73.8%) (Fig. 2). The standard BP control rate was less than 70% in the DM (69.4%) and CKD subgroups (68.5%).

Reductions in both SBP and DBP at week 24 were statistically significant ($P < 0.05$), regardless of the number of prior antihypertensive agents or the combinations of classes of prior antihypertensive agents. The degree of BP reduction was inversely proportional to the number of prior antihypertensive agents used (Fig. 3). Among the subgroups that used double-combination treatment before the study, the ARB + DU group (− 18.9/− 10.8 mmHg) had significantly ($P < 0.05$) greater mean BP reduction (SBP/DBP) than the ARB + CCB group (− 14.6/− 7.7 mmHg). Among the subgroups that used triple-combination treatment before the study, the ARB + CCB + DU group showed the lowest BP reduction (− 5.2/− 2.6 mmHg,

**Table 2** Treatment exposure

| | Effectiveness set (n = 2360) | Safety set (n = 2849) |
|---|---|---|
| Total treatment duration, days[a] | | |
| n | 2360 | 2849 |
| Mean ± SD | 197 ± 46 | 186 ± 70 |
| Median (min, max) | 185 (68, 638) | 183 (4, 1010) |
| Cumulative dose of O/A/H 20/5/12.5 mg, tablets[b] | | |
| n | 1558 | 1895 |
| Mean ± SD | 189 ± 53 | 175 ± 69 |
| Median (min, max) | 183 (1, 638) | 181 (1, 728) |
| Cumulative dose of O/A/H 40/5/12.5 mg, tablets[b] | | |
| n | 626 | 722 |
| Mean ± SD | 183 ± 63 | 174 ± 71 |
| Median (min, max) | 183 (1, 589) | 183 (1, 617) |
| Cumulative dose of O/A/H 40/10/12.5 mg, tablets[b] | | |
| n | 309 | 385 |
| Mean ± SD | 178 ± 65 | 180 ± 109 |
| Median (min, max) | 183 (1, 491) | 178 (1, 1010) |

O/A/H represents single-pill combination therapy of olmesartan, amlodipine, and hydrochlorothiazide

SD standard deviation

[a]Total treatment duration was calculated using the following formula: date of the last dose of O/A/H − date of first dose of O/A/H + 1

[b]Cumulative dose of O/A/H was calculated using the following formula: number of tablets per dose × number of doses per day × total number of treatment days

$P < 0.05$), although there was a significant change from baseline. Compared with the ARB + CCB + DU group, the ARB + CCB + BB group (− 12.3/− 5.0 mmHg) or ARB + DU + BB group (− 7.2/− 4.1 mmHg) had significantly ($P < 0.05$) greater mean BP reduction.

When the 2017 ACC/ACA guidelines were applied, the BP control rates in the subgroups with the following risk factors were relatively lower than the intensive BP control rate in the overall effectiveness population (41.4%): CKD with DM (38.6%), high-risk hypertension (37.7%), high-risk DM (37.4%), and CKD with albuminuria (28.1%) (Table 4). In the subgroups where the target SBP/DBP was < 140/90 mmHg, according to the 2022 KSH guidelines, the very elderly subgroup (≥ 80 years old) had a relatively lower BP control rate (67.1%) than the standard BP control rate in the overall effectiveness population (73.3%). The CKD without albuminuria subgroup had the highest BP control rate at 77.2%.

### Safety Outcomes

The safety outcomes are summarized in Table 5. During the 24-week follow-up period, 23.3% of patients included in the safety set (n = 2849) experienced 934 TEAEs, of which 109 events observed in 3.83% of the patients were reported as serious adverse events (SAEs). Common TEAEs (occurrence rate > 1%) included dizziness (4.32%), hypotension (1.54%), and headaches (1.44%), and the most common SAE was cerebral infarction (0.18%); none of these were considered as ADRs.

A total of 223 ADRs were observed in 7.8% of overall patients. The most common ADR was dizziness (2.91%), followed by hypotension (1.51%) and headache (0.70%). The occurrence rate of serious ADRs was 0.28%, with eight events, including two events of hyponatremia and the single event of headache, seizure, vestibular neuronitis, rib fracture, intervertebral disc protrusion, and death.

There were four deaths. Three deaths, namely due to cardiac arrest, cerebral hemorrhage, and hepatocellular carcinoma, were assessed as unlikely to be related to O/A/H. As for the one death classified as an ADR, the exact cause and date of death were unavailable, and its relationship to O/A/H was unassessable.

## DISCUSSION

This observational study identified the effectiveness and safety of O/A/H in South Korean

**Table 3** Major effectiveness outcomes

| | Effectiveness set ($n$ = 2360) | |
|---|---|---|
| | No. of patients (%) or mean ± SD | 95% CI or $p$ value |
| Primary endpoint | | |
| Intensive BP control rate at week 24[a] | 978 (41.4) | 39.5, 43.4 |
| Secondary endpoints | | |
| Standard BP control rate at week 24[b] | 1729 (73.3) | 71.5, 75.1 |
| Change in SBP/DBP at week 24 baseline (mmHg) | − 17.8 ± 20.8/− 9.3 ± 13.5 | < 0.0001/< 0.0001[c] |

BP control rates are presented as frequency and percentage with 95% CI. BP changes at week 24 from baseline are presented as mean and standard deviation

*SD* standard deviation, *BP* blood pressure, *CI* confidence interval, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

[a]Intensive BP control rate at week 24 was defined as the percentage of patients who achieved both the SBP (< 130 mmHg) and DBP (< 80 mmHg) targets at week 24

[b]Standard BP control rate at week 24 was defined as the percentage of patients who achieved both the SBP (< 140 mmHg) and DBP (< 90 mmHg) targets at week 24

[c]Statistical significance of BP change at week 24 from baseline was tested using the Wilcoxon signed-rank test

patients with hypertension and at least one additional cardiovascular risk factor. The administration of O/A/H significantly reduced mean SBP/DBP at week 24 from baseline, with a mean change of − 17.8 mmHg and − 9.3 mmHg, respectively. The reduction in BP was consistently observed across all the risk groups. Moreover, patients with hypertension and additional cardiovascular risk factors who received O/A/H to control BP sustained a mean SBP/DBP below 130/80 mmHg, the target level recommended in the current ESC/ESH guidelines, throughout the study period [10]. Notably, a significant BP reduction was observed within 4 weeks after switching to O/A/H. This relatively rapid onset of O/A/H effectiveness is worth emphasizing, given that early and fast BP management is associated with a more effective and sustained BP control, and hence with greater long-term clinical benefits [23, 24].

At the end of the study period, the standard BP control rate for the study population was 73.3% (95% CI 71.5, 75.1), which is consistent with the results of previous real-world studies of O/A/H in the general population of patients with hypertension (BP control rates 70.6–82.6%). This also corresponds well with

the published data on the percentage of South Korean patients with hypertension and uncontrolled BP (29%) [3, 16, 17]. Our study results highlighted the importance of O/A/H in reducing and sustaining BP in patients with hypertension and additional cardiovascular risk factors, a group in which BP control is considered challenging. However, the data on the O/A/H effectiveness presented herein should be interpreted with caution. The target BP for patients with additional cardiovascular risk factors was set lower than that for those without additional risk factors; hence, the beneficial effects of O/A/H in the present study might have been overestimated. Furthermore, patients with additional cardiovascular risk factors are subjected to more intensive care and close monitoring, which may lead to improved BP control.

The intensive BP control rate for the study population was 41.4% (95% CI 39.45%, 43.4%), with rates varying among different cardiovascular risk subgroups. A recent study on patients with resistant hypertension in Korea found that the average rate of achieving intensive BP control was approximately 50%, which is somewhat higher than the rate observed in our study [25]. This discrepancy can be explained by

several factors. First, the target BP for patients with resistant hypertension may differ from that for patients with hypertension and cardiovascular risk factors. While the target BP for patients with resistant hypertension is generally SBP < 130 mmHg and DBP < 80 mmHg, the 2018 KSH recommends a target SBP/DBP of < 140/90 mmHg for patients with hypertension and cardiovascular risk factors, except for those with DM and concomitant cardiovascular risk factors, high-risk hypertension, CVD, and CKD with albuminuria [5]. The relatively high target BP of the patients enrolled in the present study may have contributed to the lower intensive BP control rate. Another reason may be that some physicians might have been doubtful whether the benefits of pursuing more intensive BP control outweighed the risks in patients with hypertension and cardiovascular risk factors [20, 26–28]. Such an approach could lead to therapeutic inertia, with a resultant failure in

achieving intensive BP goals in some patients with inadequate BP control owing to the lack of timely adjustment of O/A/H treatment [17].

Subgroup analysis based on combinations of previous antihypertensive drug classes showed the efficacy of O/A/H in managing high baseline BP levels, effectively attaining target BP levels within 24 weeks in antihypertensive treatment-naïve patients (Fig. 3 and Table S3). Nevertheless, the utilization of the triple combination therapy in treatment-naïve patients continues to cause controversy. The study's protocol permits the administration of O/A/H at the physician's discretion, specifically reserved for patients necessitating a SBP reduction of 20 mmHg or more to achieve the target BP level.

The result of subgroup analysis based on combinations of previous antihypertensive drug classes also showed that patients who used a combination of one or two antihypertensive drugs before switching to O/A/H had a more
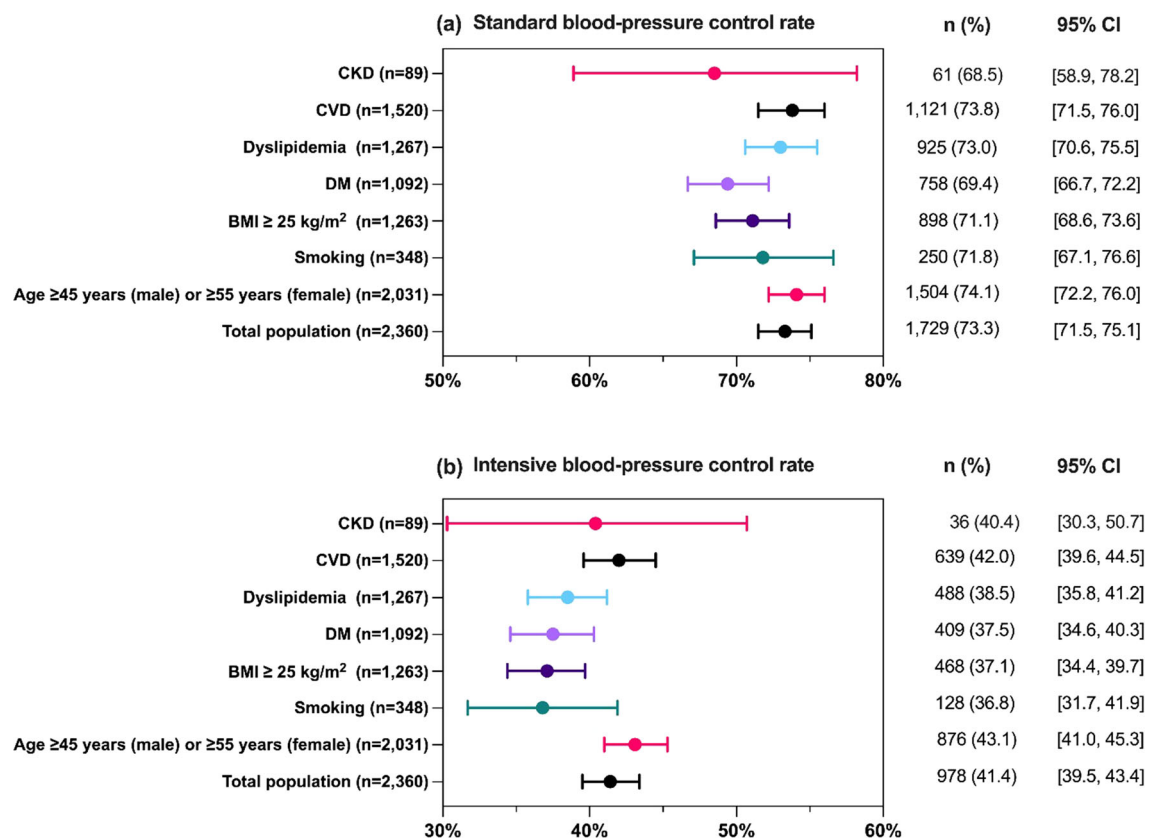


Fig. 2 Blood pressure control rates according to a the standard criteria or b intensive criteria. *BMI* body mass index, *CI* confidence interval, *CKD* chronic kidney disease, *CVD* cardiovascular disease, *DM* diabetes mellitus

significant BP reduction. These findings indicate that combining drugs from different and complementary classes provides a synergistic effect on BP reduction, which in turn leads to greater antihypertensive efficacy. Moreover, patients who switched from a combination of at least three antihypertensive agents to O/A/H showed a significant BP reduction. Interestingly, a significant BP reduction was also documented in a subgroup of patients in whom O/A/H was introduced instead of ARB + CCB + DU, the free combination of agents from the same groups as SPC components. This finding supports the use of SPC to improve medication adherence and BP control. However, any conclusion on this matter should be formulated carefully as the introduction of O/A/H may also be associated with dose escalation.

Both DM and metabolic syndrome are potent cardiovascular risk factors, and the 2022 KSH guidelines recommend intensive BP control (< 130/80 mmHg) for patients with high-risk DM, defined as DM accompanied by asymptomatic organ damage or a cardiovascular risk factor [22]. In the present study, intensive and standard BP control rates in patients with DM were lower than those in the overall population. Patients with hypertension and DM require multiple medications, including antihypertensive and antidiabetic drugs, and this polypharmacy may negatively affect their medication adherence compared with other cardiovascular risk factors. Poor medication adherence in patients with hypertension and DM can interfere with achievement of the target BP. Furthermore, most of the participants with DM included in this study (1087 out of 1092, 99.5%) were classified as having high-risk DM and thus might present with kidney-related complications; in these cases adequate BP control is generally more challenging. A relatively poor BP control rate in patients with DM and/or CKD was also observed in patients who received more than two antihypertensive drugs in a cross-sectional study [29]. Although SPC is beneficial for BP control by improving medication adherence, further studies are needed to investigate the risk factors that interfere with BP control in patients with hypertension and DM and/or CKD because SPC could be only one of the many prescribed medications in patients with polypharmacy. Therefore, physicians should care more closely for patients with hypertension and additional cardiovascular risk factors and monitor their BP to ensure adequate control.

Within this study, patients who exhibited SBP below 130 mmHg were included. Those were found to be previously utilizing a regimen consisting of three or more antihypertensive medications. In the case of these patients, the utilization of SPC therapy, such as the combination of O/A/H, could be considered as a means to enhance treatment adherence. In addition, the study included 26.9% of patients with controlled hypertension (Table 1). The classification of patients with uncontrolled hypertension was based on the criteria of SBP exceeding 140 mmHg and DBP exceeding 90 mmHg. However, it is important to note that this study focused on patients with hypertension and concurrent CV risk factors, including those with high-risk DM, high-risk CVD, and high-risk hypertension. KSH guidelines recommended a lower target BP of less than 130 mmHg for SBP and 80 mmHg for DBP in these patient groups. Given the lower target BP in these patients, switching to higher dose O/A/H SPC than the doses of the free combination could be considered when switching to O/A/H SPC.

The majority of patients with hypertension previously using the combinations of ARB + CCB + BB and ARB + DU + BB had received O/A/H as an additive to BB, with some entirely switching to O/A/H therapy (Table 1). For those patients who underwent the switching to O/A/H, it is postulated that such changes were based on clinical judgment, likely due to the absence of relevant medical histories warranting the continued use of BB, such as a history of myocardial infarction or heart failure. Furthermore, it is contemplated that in cases where there exists a potential risk of edema associated with the usage of ARB + CCB + BB combinations, the substitution of diuretics instead of BB may be deemed an appropriate therapeutic consideration.

This study was conducted in a group of patients with hypertension and additional
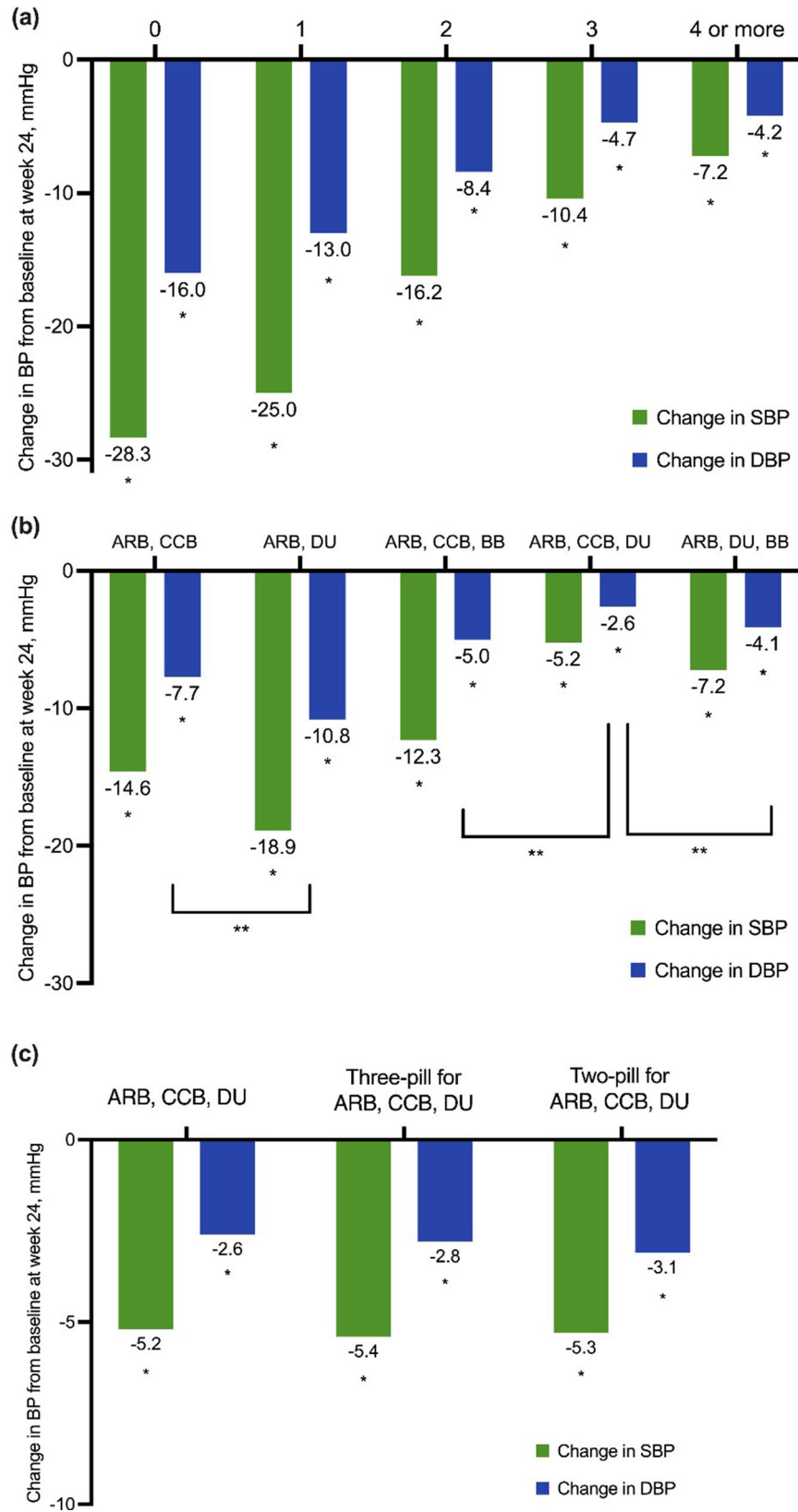
◄**Fig. 3** Subgroup analysis for mean change in BP at week 24 from baseline. **a** Subgroups are based on the number of classes of previous antihypertensive agents. **b** Subgroups are based on the combinations of classes of antihypertensive agents taken prior to the study. **c** Mean BP change in the subgroup of patients using the triple combination of ARB, CCB, and DU before the study is presented. *ARB, CCB refers to the subgroup of patients using ARB, CCB combination treatment before the study. †ARB, DU refers to the subgroup of patients using ARB, DU combination treatment before the study. ‡ARB, CCB, BB refers to the subgroup of patients using ARB, CCB, BB combination treatment before the study. §ARB, CCB, DU refers to the subgroup of patients using ARB, CCB, DU combination treatment before the study. ‖ARB, DU, BB refers to the subgroup of patients using ARB, DU, BB combination treatment before the study. ¶Three-pill for ARB, CCB, DU refers to the subgroup of patients using three individual pills for ARB, CCB, and DU combination treatment before the study. ◇Two-pill for ARB, CCB, DU refers to the subgroup of patients using two individual pills for ARB, CCB, and DU combination treatment before the study. ↓A single-asterisk sign (*) indicates $P < 0.05$ versus the baseline and a double-asterisk sign (**) indicates $P < 0.05$ versus the comparator group. *ARB* angiotensin receptor blocker, *BB* beta-blocker, *BP* blood pressure, *CCB* calcium channel blocker, *DU* diuretic, *DBP* diastolic blood pressure, *SBP* systolic blood pressure

cardiovascular risk factors. As previously mentioned, the target BP values in such patients are set lower than in those without concomitant risks. Although the more aggressive approach to antihypertensive treatment in patients with additional cardiovascular risk factors might theoretically lead to higher frequency of side effects associated with hypotension, the hypotension rate in the present study (1.51%) was within the range reported in previous studies on patients with similar characteristics (0.6–2.4%) [12–14, 16, 17, 30]. An extension study of the TRINITY trial also showed that ADRs occurring in patients with additional cardiovascular risk were consistent with the established safety profile of O/A/H [15]. This implies that safety concerns should not constitute an argument against pursuing more aggressive BP targets in patients with additional cardiovascular risk.

During the observation period, the incidence of edema associated with O/A/H use was approximately 0.3% among patients included in the effective dataset. Among the subgroup of 385 patients taking 40/10/12.5 mg of O/A/H containing 10 mg of amlodipine, six patients (1.5%) experienced edema due to O/A/H administration. In comparison, a previous study by Guthrie reported a significantly higher edema incidence of 10.8% in a subset using an SPC of telmisartan and amlodipine 10 mg [30]. The lower edema incidence observed in the present study is likely due to the exclusion of patients who had previously experienced edema while using CCB before switching to O/A/H. Notably, among patients without prior CCB use (535 patients), the incidence of edema with O/A/H was 1.1%, higher than the overall incidence of 0.3%. These findings suggest that physicians may have opted to prescribe O/A/H to patients, considering the potential risk of edema associated with CCB usage. Furthermore, the low incidence of edema observed in this study may be attributed to the concurrent administration of hydrochlorothiazide, which possesses diuretic properties.

During this study, a dropout rate of 22% (701 subjects) was observed among the enrolled patients, attributed to various factors. One primary reason was the loss to follow-up, possibly caused by enrolled patients' non-compliance with scheduled medical visits at tertiary general hospitals, reflecting the influence of the Korean healthcare delivery system's discouragement of frequent hospital visits solely for obtaining antihypertensive medications. Additionally, some cases resulted in discontinuation of O/A/H therapy, with reasons ranging from patient reluctance to adhere to the treatment regimen to the occurrence of adverse events related to O/A/H use. Notably, the incidence of serious adverse events during the study was relatively low, indicating that drug intolerance may not have been the primary cause of O/A/H discontinuation (Table 5).

Some potential limitations of the present study should be considered. First, this was a non-interventional, prospective observational study without a comparator group, rather than a randomized controlled study. Underreporting

**Table 4** Blood pressure change at week 24 from baseline and blood pressure control rate in each subgroup with different cardiovascular risk factors

| Clinical conditions | No. of patients | SBP/DBP, mmHg | | | p value | 2022 KSH guidelines | | | 2017 ACC/AHA guidelines | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Baseline | At week 24 | Change from baseline at week 24 | | BP target | BP control rate at week 24[a] n (%) | 95% CI | BP target | BP control rate at week 24[a] n (%) | 95% CI |
| Total population | 2360 | 146.9 ± 17.9/ 83.9 ± 13.3 | 129.0 ± 15.6/ 74.7 ± 11.3 | − 17.8 ± 20.8/− 9.3 ± 13.5 | < 0.0001/ < 0.0001 | < 140/ 90 | 1729 (73.3) | 71.5, 75.1 | < 130/ 80 | 978 (41.4) | 39.5, 43.4 |
| Elderly (≥ 65 years) | 1161 | 148.2 ± 18.2/ 79.8 ± 12.4 | 129.6 ± 16.0/ 71.2 ± 11.0 | − 18.6 ± 22.1/− 8.7 ± 13.4 | < 0.0001/ < 0.0001 | < 140/ 90 | 835 (71.9) | 69.4, 74.4 | < 130/ 80 | 504 (43.4) | 40.6, 46.3 |
| Very elderly (≥ 80 years) | 234 | 151.8 ± 19.8/ 77.2 ± 12.4 | 130.9 ± 16.7/ 70.0 ± 11.8 | − 20.8 ± 23.0/− 7.3 ± 13.7 | < 0.0001/ < 0.0001 | < 140/ 90 | 157 (67.1) | 61.1, 73.1 | < 130/ 80 | 97 (41.5) | 35.1, 47.8 |
| High-risk hypertension[b] | 1220 | 146.1 ± 16.9/ 83.6 ± 12.4 | 130.1 ± 15.1/ 74.9 ± 11.0 | − 16.0 ± 19.5/− 6.7 ± 12.8 | < 0.0001/ < 0.0001 | < 130/ 80 | 460 (37.7) | 35.0, 40.4 | < 130/ 80 | 460 (37.7) | 35.0, 40.4 |
| High-risk DM[c] | 1087 | 146.7 ± 17.0/ 82.9 ± 12.5 | 130.8 ± 15.7/ 74.4 ± 11.0 | − 15.9 ± 19.6/− 8.5 ± 12.9 | < 0.0001/ < 0.0001 | < 130/ 80 | 407 (37.4) | 34.6, 40.3 | < 130/ 80 | 407 (37.4) | 34.6, 40.3 |
| CVD | 1520 | 145.9 ± 18.3/ 82.8 ± 13.4 | 128.4 ± 15.1/ 74.2 ± 11.2 | − 17.5 ± 20.8/− 8.6 ± 13.7 | < 0.0001/ < 0.0001 | < 140/ 90 | 1121 (73.8) | 71.5, 76.0 | < 130/ 80 | 639 (42.0) | 39.6, 44.5 |
| High-risk CVD[d] | 1216 | 145.8 ± 18.3/ 82.1 ± 12.8 | 128.4 ± 14.9/ 73.5 ± 10.7 | − 17.4 ± 20.7/− 8.6 ± 13.2 | < 0.0001/ < 0.0001 | < 130/ 80 | 525 (43.2) | 40.4, 46.0 | < 130/ 80 | 525 (43.2) | 40.4, 46.0 |
| Stroke | 383 | 148.3 ± 18.8/ 83.6 ± 13.8 | 127.4 ± 14.9/ 72.7 ± 11.1 | − 20.9 ± 20.8/− 10.9 ± 14.6 | < 0.0001/ < 0.0001 | < 140/ 90 | 289 (75.5) | 71.2, 79.8 | < 130/ 80 | 192 (50.1) | 45.1, 55.1 |
| CKD without albuminuria | 57 | 148.6 ± 18.4/ 81.4 ± 14.1 | 127.1 ± 16.1/ 71.4 ± 11.2 | − 21.5 ± 23.0/− 10.0 ± 13.7 | < 0.0001/ < 0.0001 | < 140/ 90 | 44 (77.2) | 66.3, 88.1 | < 130/ 80 | 27 (47.4) | 34.4, 60.3 |
| CKD with albuminuria | 32 | 150.4 ± 18.9/ 79.8 ± 14.8 | 138.6 ± 17.9/ 73.7 ± 13.1 | − 11.8 ± 24.5/− 6.1 ± 17.2 | 0.0105/0.0552 | < 130/ 80 | 9 (28.1) | 12.6, 43.7 | < 130/ 80 | 9 (28.1) | 12.6, 43.7 |

**Table 4** continued

| Clinical conditions | No. of patients | SBP/DBP, mmHg | | | | 2022 KSH guidelines | | | 2017 ACC/AHA guidelines | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Baseline | At week 24 | Change from baseline at week 24 | p value | BP target | BP control rate at week 24[a] n (%) | 95% CI | BP target | BP control rate at week 24[a] n (%) | 95% CI |
| CKD with DM | 70 | 148.0 ± 18.1/ 79.6 ± 13.2 | 134.1 ± 17.6/ 72.4 ± 12.4 | − 13.9 ± 22.3/ − 7.3 ± 14.3 | < 0.0001/ < 0.0001 | < 130/ 80 | 27 (38.6) | 27.2, 50.0 | < 130/ 80 | 27 (38.6) | 27.2, 50.0 |

Continuous variables are presented as means and standard deviations and categorical variables as frequencies and percentages

*SBP* systolic blood pressure, *DBP* diastolic blood pressure, *KSH* Korean Hypertension Society, *ACC/AHA* American College of Cardiology and American Heart Association, *BP* blood pressure, *CI* confidence interval, *DM* diabetes mellitus, *CVD* cardiovascular disease, *CKD* chronic kidney disease

[a]BP control rate at week 24 was defined as the percentage of patients who achieved both SBP and DBP targets for each guideline

[b]Patients with high-risk hypertension were defined as those with at least three cardiovascular risk factors, including age (≥ 45 years in men, ≥ 55 years in women), smoking, dyslipidemia, BMI ≥ 25 kg/m$^2$, and DM

[c]Patients with high-risk DM were defined as those with DM as well as high-risk CVD or at least one risk factor

[d]Patients with high-risk CVD were defined as those aged ≥ 50 years with coronary artery disease, peripheral vascular disease, abdominal aortic aneurysm, heart failure, or left ventricular hypertrophy

**Table 5** Summary of adverse events

| | Safety set ($n$ = 2849) | |
|---|---|---|
| | No. of patients (%) | No. of events |
| TEAEs | 663 (23.27) | 934 |
| Dizziness | 123 (4.32) | 126 |
| Hypotension | 44 (1.54) | 44 |
| Headache | 41 (1.44) | 41 |
| Edema or edema peripheral | 17 (0.60) | 17 |
| ADRs | 223 (7.83) | 264 |
| Dizziness | 83 (2.91) | 85 |
| Hypotension | 43 (1.51) | 43 |
| Headache | 20 (0.70) | 20 |
| Edema or edema peripheral | 7 (0.25) | 7 |
| Unexpected TEAEs | 322 (11.30) | 408 |
| Unexpected ADRs | 56 (1.97) | 61 |
| Serious TEAEs | 109 (3.83) | 117 |
| Cerebral infarction | 5 (0.18) | 5 |
| Serious ADRs | 8 (0.28) | 8 |
| Hyponatremia | 2 (0.07) | 2 |
| Death | 1 (0.04) | 1 |

*TEAEs* treatment-emergent adverse events, *ADRs* adverse drug reactions

is unavoidable in such a study design, which may lead to a potential bias. Also, the present study is not able to establish causality, as it cannot control for all potential confounding variables, and it is unable to manipulate exposure or intervention. Therefore, our findings must be interpreted with caution and in conjunction with other studies. Additionally, variables related to routine care (such as the use of concomitant medications) were left to the discretion of the individual physicians in charge. All these factors, which could not be controlled under a real-world study design, should be considered as potential confounders influencing the results. Second, the treatment period was relatively short. If the treatment period were longer, the effect of O/A/H on BP would probably be even more pronounced. Despite these potential limitations, the results of the present study provide real-world evidence for the beneficial effects of O/A/H in a large sample of patients with hypertension and additional cardiovascular risk factors, in whom BP control is generally considered a challenge.

## CONCLUSION

The use of O/A/H, a triple SPC therapy, resulted in a rapid and sustained reduction in SBP/DBP in South Korean patients with hypertension and additional cardiovascular risk factors. O/A/H was safe and well tolerated by the study population. However, it is imperative to acknowledge that the study design employed was that of a prospective observational nature, lacking a comparator group. Therefore, prudent consideration and cautious interpretation of the clinical implications of the findings are warranted. It is also important to recognize that further investigations may be necessary to corroborate and validate the results obtained from this study.

## ACKNOWLEDGEMENTS

## Declarations

*Ethical Approval.* The study protocol and informed consent forms were approved by the institutional review board (IRB) of each participating institution. The study was registered with the Clinical Research Information Service (KCT0003401; [https://cris.nih.go.kr/cris/search/detailSearch.do/20795](https://cris.nih.go.kr/cris/search/detailSearch.do/20795)). The study was conducted in accordance with the principles of the Declaration of Helsinki 1964 and its later amendments as well as the rules of each IRB. All patients voluntarily provided written informed consent before enrollment in the study. Data were de-identified to protect the privacy of the participating patients and to be fully compliant with locally applicable regulations.

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